King's College London Neuroscience Society

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Neurosphere

NEUROSOC
KING'S COLLEGE LONDON

TOUCHING THE BRAIN

National Conference 2021

Deep Brain Stimulation

A new therapeutic frontier

Brain-Computer Interfaces

The future of Man & Machine

Cover Art: Hamaad Khan

Editors' Welcome

"The Brain—is wider than the sky" wrote Emily Dickinson - and how true. As students of neuroscience, we get to explore its limitless horizon stretching over neurology, philosophy of the mind, psychiatry and so much more. Look past the sulci and gyri, and you'll find yourself staring inward, asking deep-pitted questions of identity; of who we are and how we are.

Through its infinite intricacy, the brain offers us our world. It's the lens through which we see ourselves and others. Our brain can feel as if it is our own, only until it slips past our clutch, succumbing to external influences of addiction, dementia, schizophrenia or even falling in love. It is this biological vulnerability that has offered scientists and students alike an enjoyment in the study of neuroscience.

We are so excited to offer you this new magazine. Our aim at Neurosphere is to unravel this knot of neurons that we call the human brain, to seek a better understanding of it and impart some of our excitement to you - our dear reader. In this first edition, we are taking on the theme of our annual conference "touching the brain", and looking at new technologies that are transforming our understanding of the brain. Whether it be brain computer interfaces or deep brain stimulation, we are proud to present the work of our incredible authors.

If you would like to contribute to future editions or write for our online blog, do get in touch. We are always looking for enthusiastic individuals.

We hope you enjoy it!

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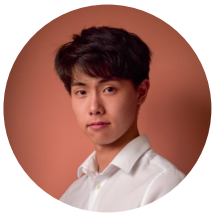

Daniel Shao
Editor (Magazine)

Hamaad Khan
Editor (Website)

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President's Welcome

Modern neuroscience spans an ever growing number of domains and more than ever calls for collaboration. In the public eye neuroscience is seemingly uncovering secrets to some of the greatest quandaries, but the reality is that we are still many light years away.

The Neuroscience Society of KCL aims to expose these truths and establish a network of thought, discussion and education. This year each member of the committee has worked hard to develop these goals in spite of the limitations. I am grateful to every one of them.

We have also established a digital space to curate contributions from members beyond the committee. Thank you to all those who have submitted their ideas and writings as these generate further thought and progress. This magazine is the spearhead of this initiative, and I hope that future issues will continue to gather work from a wide range of thinkers - neuroscientists, philosophers, medics and beyond..!

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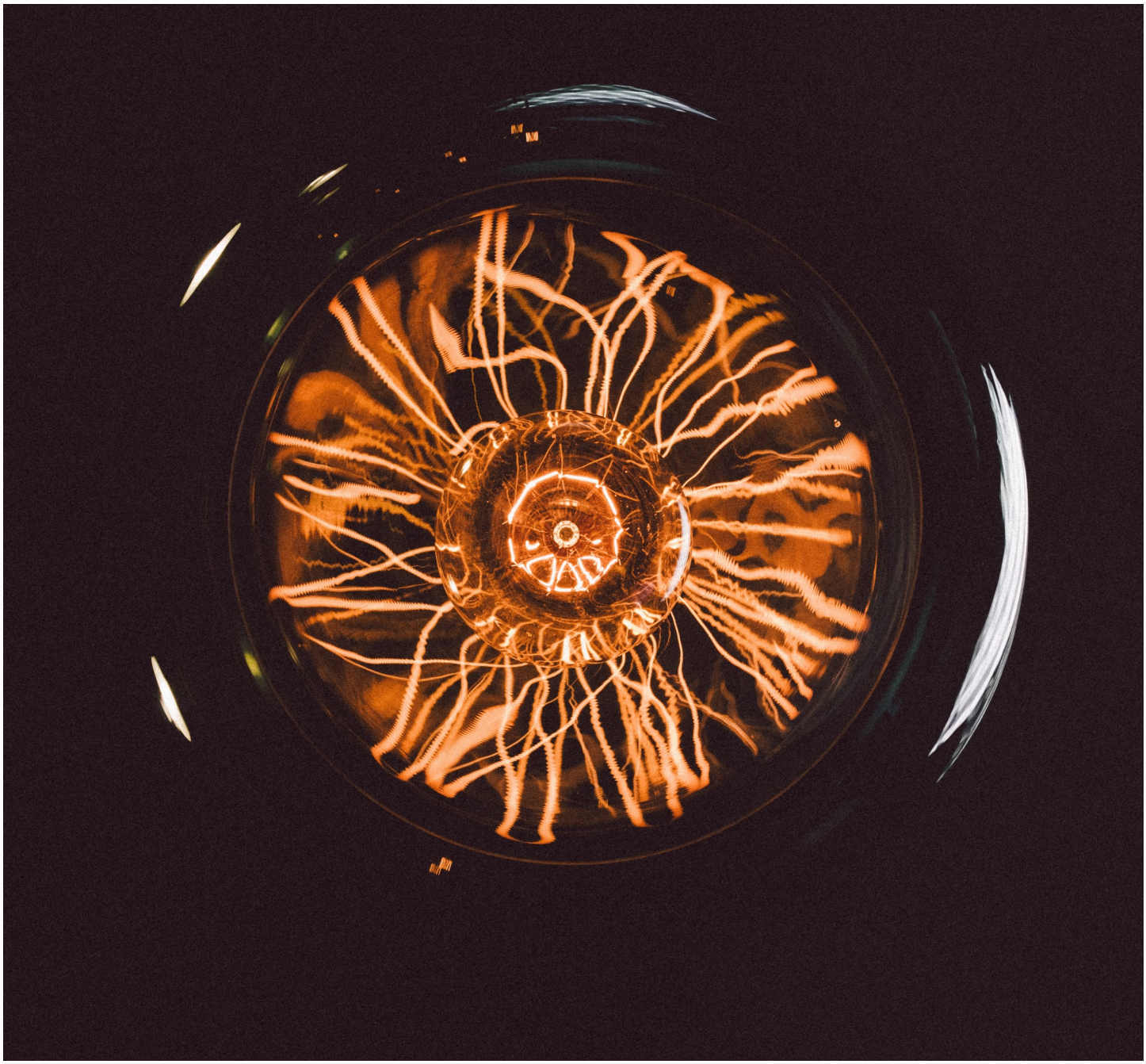
Deep Brain Stimulation



"When the Visual Cortex is Everything but Visual"

Rita Bertani
BSc Neuroscience

Transcranial magnetic stimulation (TMS) is a type of neurotechnology which can change the magnetic field of the brain by applying a coil to the scalp. Thanks to TMS, researchers can activate or disrupt activity in specific areas of the brain and understand more about the function of these areas by observing changes in the perception and behaviour of their participants[1]. Apart from its use in basic neuroscience research, TMS has interesting clinical applications, such as being one of the possible treatments for drug-resistant depression in the United Kingdom[2]. In this short article, I will focus on the use of TMS to investigate functional cross-modal plasticity of the occipital – "visual" – cortex, hoping to offer a glimpse into the excitement surrounding this research area.

An influential positron emission tomography (PET) study has revealed activation of the primary and secondary visual cortices during Braille reading in early blind subjects[3]. These quite exciting findings, which show that tactile information is not always and only processed in primary reception areas for touch (Brodmann areas 3, 1 and 2), were confirmed by a TMS study[4]: Cohen and colleagues used TMS to disrupt the activity of the occipital cortex of blind subjects, which resulted in blind people struggling to read Braille or embossed Roman letters; these difficulties were not observed when stimulating the occipital cortex of sighted controls. These and similar studies suggest that the occipital cortex, when deprived of visual inputs, learns to respond to stimuli in other sensory modalities, and that this area of the brain is involved in reading and language processing regardless of the sense employed to convey linguistic information.

Apart from being activated during Braille reading, the "blind visual cortex" seems to be involved in episodic memory[5], auditory processing[6,7] and

tactile exploration of objects[8]. In a study by Kupers et al.[9], both blind and sighted participants were trained with a tongue display unit (TDU) – a neural interface which captures an image from the environment and converts it to tactile stimulation of the tongue, enabling users to "see" with the sense of touch[10]; when stimulated via TMS over the occipital cortex, blind subjects reported tactile sensations that referred to the tongue, while sighted subjects reported visual phosphenes. These findings bring further evidence for an involvement of the blind occipital cortex in non-visual sensory processing.

To explain the extraordinary functional properties of the "blind visual cortex", researchers such as Burton[11] have hypothesized that in people born blind or deprived of vision from an early age, new connections – parietooccipital, for example – are established between areas of the brain which are not directly or strongly connected in sighted subjects; alternatively, these connections could exist in every human being, including the sighted, but they may be inhibited in the presence of vision and only able to fully develop and become active when vision is lost.

This type of neural plasticity, which results in specific sensory inputs being processed in areas of the brain which are normally devoted to other sensory modalities, is called cross-modal plasticity, and it is often mentioned in support of cortical deference and against cortical dominance – in other words, cross-modal plasticity seems to demonstrate that the qualitative character of experience is determined by the type of input to a brain area (deference), and not by the activation of a specific brain area itself (dominance)[4,9,12]. However, the means by which an area of the brain is reorganized to process a specific sensory input rather than nother are still not fully understood. Further studies on the occipital cortex of the blind could provide us with some answers.

References

1. Society, R., iHuman: Blurring Lines Between Mind and Machine. 2019: Royal Society.

2. Janicak, P.G. and M.E. Dokucu, Transcranial magnetic stimulation for the treatment of major depression. Neuropsychiatric disease and treatment, 2015. 11: p. 1549-1560.

3. Sadato, N., et al., Activation of the primary visual cortex by Braille reading in blind subjects. Nature, 1996. 380(6574): p. 526-8.

4. Cohen, L.G., et al., Functional relevance of cross-modal plasticity in blind humans. Nature, 1997. 389 (6647): p. 180-183.

5. Raz, N., A. Amedi, and E. Zohary, V1 activation in congenitally blind humans is associated with episodic retrieval. Cereb Cortex, 2005. 15(9): p. 1459-68.

6. Kujala, T., et al., Visual cortex activation in blind humans during sound discrimination. Neuroscience Letters, 1995. 183(1): p. 143-146.

7. Weeks, R., et al., A positron emission tomographic study of auditory localization in the congenitally blind. J Neurosci, 2000. 20(7): p. 2664-72.

8. Amedi, A., et al., Cortical activity during tactile exploration of objects in blind and sighted humans. Restorative Neurology and Neuroscience, 2010. 28: p. 143-156.

9. Kupers, R., et al., Transcranial magnetic stimulation of the visual cortex induces somatotopically organized qualia in blind subjects. Proceedings of the National Academy of Sciences, 2006. 103(35): p. 13256.

10. Kaczmarek, K.A., The tongue display unit (TDU) for electrotactile spatiotemporal pattern presentation. Sci Iran D Comput Sci Eng Electr Eng, 2011. 18(6): p. 1476-1485.

11. Burton, H., Visual Cortex Activity in Early and Late Blind People. The Journal of Neuroscience, 2003. 23(10): p. 4005.

12. Kupers, R., et al., The Nature of Consciousness in the Visually Deprived Brain. Frontiers in Psychology, 2011. 2: p. 19.

“Animal Electricity in Cardiology versus Neurology”

Nye Rhys Potter
MBBS Medicine

Electrical currents in biology were recognised long before electric currents in wires. In 1780 Luigi Galvani discovered that a dead frog’s legs twitched when struck by an electrical spark. He went on to propose that animals generate their own “animal electricity” that behaved like the animal spirits believed to control behaviour by Aristotle, Galen and Descartes. Galvani was one step closer to the truth. Subsequent science showed that the control of behaviour was electrical. In 1852 von Helmholtz measured the speed of a frog nerve impulse to 27 meters/second and in 1952 Hodgkin and Huxley demonstrated how the nervous current was a combination of Na^+ and K^+ currents passing through the cellular membrane.

Meanwhile, the similarities between animal and artificial electricity meant that at each stage of this scientific development there were researchers who sought to use electricity as medicine. Galvani applied current directly to a paralysed man and observed him turning his head. This was later tried on a cadaver by his nephew Giovani Aldini on a cadaver where he observed the limp dead boy sat upright, as if momentarily brought back to life. Of course, this went on to inspire the young Mary Shelly to kickstart the genre of science fiction with the writing of The Modern Prometheus or Frankenstein.

Medicine is often less about treatment than diagnosis and even if early electrical pioneers wanted to jump to resurrection some of the longest-lasting impacts on medicine came with the development of the electrocardiogram (ECG). This was a detection of the electrical activity of the heart and is currently one of the most frequently used medical investigation in hospitals. The first human electrocardiogram was performed by Augustus D. Waller at St Mary's in 1887. Though it was only named as such by Einthoven in 1893, who went on to win the 1924

Nobel Prize for his work. This discovery led to numerous diagnostic uses and arguably hastened the arrival of two treatments, the pacemaker, a regular electrical current that can reset the heartbeat and the defibrillation a dose of electrical current that can restart the heart into a healthier cycle.

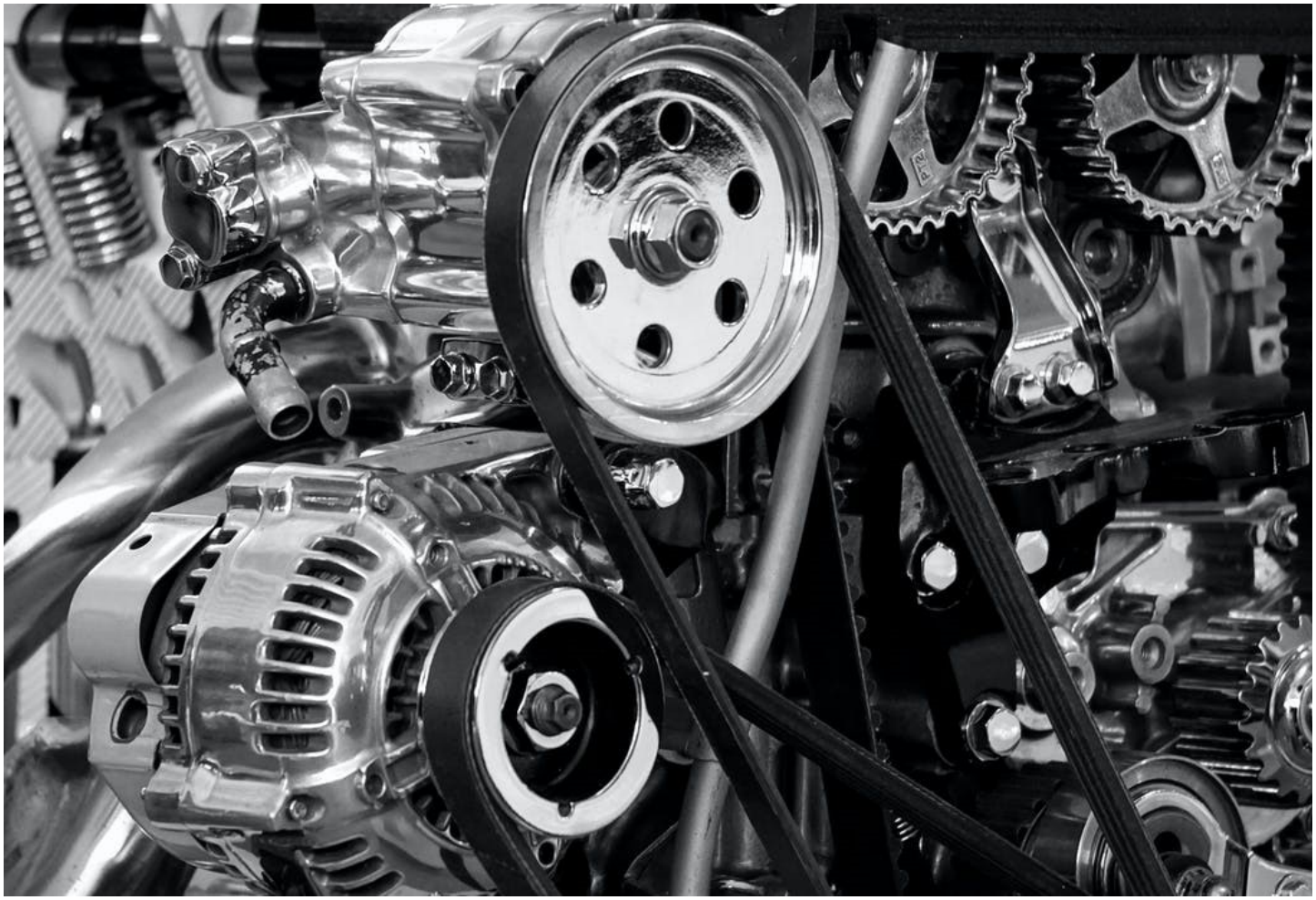
It took a lot longer for the electroencephalogram (EEG) to be invented by a psychiatrist, Hans Berger in 1926. Even though electrical activity was known to be fundamental to brain diseases such as in epilepsy by John Hughlings Jackson in 1873. As it stands today ECGs are one of the most fundamental skills taught in medical school while EEGs are barely on the curriculum. Further still precipitation of interventions from EEG research has not touched the success of the pacemaker or defibrillator in cardiology. However, in recent decades there are interesting parallels. In so far as epilepsy is a dyssynchronous discharge of electrical activity it shares some similarity with heart dysrhythmias, which are treated with pacemakers. The development of deep-brains stimulation and vagus nerve stimulation serve to regulate these brain dysrhythmias and the devices occupy an important niche for drug-resistant epilepsy subtypes. On the other hand, brain defibrillation may seem dangerous but has a well-established role in psychiatry. Electroconvulsive therapy has some of the best outcomes of any medical intervention when used for depression. In fact this therapy has come full circle and shown some success in a similar context as cardiac defibrillation in the treatment of a continuous epileptic seizure, status epilepticus.

From a doctor's perspective cardiology and neurology show important parallels. Some of the most common disorders in each are either vascular in nature (heart attacks, strokes) or electrical (dysrhythmias, epilepsy). But from a historian's perspective the last century has been a success story for cardiologists, whereas the modern neurologist is stereotyped as "a brilliant, forgetful man with a bulging cranium, a loud bow tie… adores diagnosis and rare syndromes, and—most importantly—never bothers about treatment". There are undoubtedly many reasons why the electrical revolution precipitated success in cardiology much earlier than neurology, but maybe this coming century will change that. Though the "decade of the brain" is over the high profile of the neurosciences and the work within those fields far outstrips the equivalent scientists working on the heart. Maybe the next century will be the century of neurology.

References

1. Shock and Awe: The Story of Electricity [Internet]. Youtube. 2020 [cited 12 February 2021]. Available from: https://www.youtube.com/watch?v=Gtp51eZkwoI

2. Neurology for the masses. BMJ. 1999;319(7206):0-0.



“An Introduction to STN-DBS for Parkinson’s Disease”

Ruby Morton
BSc Psychology

Parkinson’s disease (PD) is a neurodegenerative disorder caused by the deterioration of dopaminergic (DA) neurons in the nigrostriatal pathway, one of the four major dopamine pathways in the brain. Located within the basal ganglia’s circuitry, the pathway connects the substantia nigra (SNc) to the dorsal striatum and plays a crucial role in motor function. PD is typified by motor disturbances, such as tremor, involuntary movement (dyskinesia), and reduced movement (hypokinesia), together with non-motor symptoms, including depression and cognitive deficit. The debilitating condition causes marked impairments within many areas of sufferers’ everyday lives, and is currently prevalent in 1% of people aged above 65 years, yet cases are expected to increase due to our aging population. PD is a costly condition to live with in every way – in 2017, the estimated economic burden of PD was $51.9 billion in the USA and is projected to exceed $79 billion by 2037.

Traditionally, PD has been treated with selective lesions or DA agonist medication, such as levodopa, in order to partially restore dopaminergic function lost through neuronal decay. Neuroablative lesions sever connections between problematic brain areas with varying precision and effectiveness, whereas DA agonists work by mimicking dopamine in the brain and binding to DA receptor sites to compensate for the patient underproducing the neurotransmitter. However, both treatments can induce counterintuitive effects, notably psychiatric disturbances, cognitive deficits and levodopa-induced dyskinesias. In line with the progressive nature of PD, DA agonists are most beneficial in the early stages of the disease and become less effective as neuronal degeneration and motor complications worsen. Therefore, alternative treatments for PD are of increasing importance for patients and to the wider scientific community.

Deep brain stimulation (DBS) is an emerging treatment that can also assist in alleviating Parkinsonian symptomology. DBS is a reversible surgical procedure in which implanted electrodes are used to directly stimulate specific brain areas[3]. For dyskinesia reduction in PD, typically the subthalamic nucleus (STN) or the internal globus pallidus (GPi) are targeted to inhibit neural activity through chronic high-frequency bilateral stimulation, with minimal differences in motor and mood outcomes observed between the two target areas. Stereotaxic apparatus, as well as magnetic resonance imaging, are used for the accurate installation of electrodes within the GPi or STN. DBS is more effective than current lesion-based interventions for improving Parkinsonian symptoms with fewer reported side effects, especially when placed to stimulate the dorsolateral border zone of the STN, as this delivers the most advantageous results for motor improvements and energy consumption by the electrodes.

One of the benefits of DBS is that, unlike selective lesions, it causes minimal tissue damage. Even without stimulation, the surgical insertion of the electrodes has a micro-lesioning effect on the brain and can provide an immediate improvement of symptoms following the procedure[8]. STN-DBS can vastly improve the quality of patients' lives; in the 5 years following STN-DBS treatment, postoperative studies have found that patients' motor function increases by around 50%. Additionally, STN-DBS is more effective than levodopa for treating tremor and can also work to undo levodopa-induced dyskinesias. Unlike stimulation of the GPi, STN-DBS allows for stimulation amplitudes to be gradually increased while DA agonist dosages can be slowly reduced, providing an opportunity for patients to minimise medication usage and thus the incidence of potentially aversive side effects.

Despite the aforementioned benefits, STN-DBS comes with costs. Notably, the requirement of rigorous postoperative monitoring of patients due to a higher incidence of mood disturbances associated with rapid levodopa withdrawal. Another drawback of DBS is that it can only treat motor-related issues and not the cognitive symptoms seen in PD; and while it doesn't reduce overall cognition, it's still unclear whether DBS exerts any neuroprotective effects[8]. Additionally, the long-term psychiatric effects of STN-DBS remain largely unknown. Even with prior neuropsychiatric evaluations of DBS candidates, adverse effects such as mood swings and apathy have been frequently observed in patients during the postoperative recovery period; with a minority suffering from mania, depression, or psychosis. Startlingly, up to 2% of STN-DBS patients attempt suicide, which highlights the importance of attentive preoperative screening and psychiatric follow-up for patients ensuing the procedure. Furthermore, STN-DBS doesn't always reinstate social adjustment or independence, especially for patients who have already suffered severe mobility and psychosocial impairment. Currently, effective DBS treatment relies upon suitable patient selection in order to mitigate detrimental effects, yet this strict screening criteria could be limiting its potential for use.

Overall, STN-DBS is a newly established procedure for PD, providing patients with an effective treatment for parkinsonian motor-related symptoms as well as an opportunity to reduce DA agonist medication usage. However, neither levodopa or DBS are free from side effects, and their potential benefits must be weighed against the intensive medical provision often required for patients undergoing treatment. Pharmacological interventions and selective lesions have been well-researched through their many years of implementation. Yet, for a treatment that has only been developed for the past two decades, STN-DBS shows equally promising results for the treatment of PD.

References

1. Hughes AJ, Ben-Shlomo Y, Daniel SE, Lees AJ. What features improve the accuracy of clinical diagnosis in Parkinson's disease: a clinicopathologic study. 1992. Neurology. 2001 Nov;57(10 Suppl 3): S34-8. PMID: 11775598.

2. Redgrave P, Rodriguez M, Smith Y, et al. Goal-directed and habitual control in the basal ganglia: implications for Parkinson's disease. Nat Rev Neurosci. 2010 Oct;11: 760–772. https://doi.org/10.1038/nrn2915

3. Carlson NR. Foundations of behavioral neuroscience. 9th Edition. Harlow: Pearson New International Foundation, 2014. 419-22.

4. Parkinson's UK. The incidence and prevalence of Parkinson's in the UK: results from the Clinical Practice Research Datalink Summary report. [Internet]. 2017 [cited 2021 Feb 6]. Available from: https://www.parkinsons.org.uk/sites/default/files/2018-01/CS2960%20Incidence%20and%20prevalence%20report%20branding%20summary%20report%20Published%202017.pdf

5. Yang W, Hamilton JL, Kopil C, Beck JC, Tanner CM, Albin RL, Ray Dorsey E, Dahodwala N, Cintina I, Hogan P, Thompson T. Current and projected fu-

ture economic burden of Parkinson's disease in the U.S. npj Parkinson's Disease. 2020 Jul;6 (15). https://doi.org/10.1038/s41531-020-0117-1

6. Okun MS, Vitek JL. Lesion therapy for Parkinson's disease and other movement disorders: update and controversies. Mov Disord. 2004 Apr;19(4):375-89. doi: 10.1002/mds.20037. PMID: 15077235.

7. Brooks, DJ. Dopamine agonists: their role in the treatment of Parkinson's disease. J Neurol Neurosurg Psychiatry. 2000;68: 685-690. http://dx.doi.org/10.1136/jnnp.68.6.685

8. Groiss SJ, Wojtecki L, Südmeyer M, Schnitzler A. Deep brain stimulation in Parkinson's disease. Ther Adv Neurol Disord. 2009 Nov;2(6):20-8. doi: 10.1177/1756285609339382. PMID: 21180627; PMCID: PMC3002606.

9. Okun MS, Fernandez HH, Wu SS, Kirsch-Darrow L, Bowers D, Bova F, Suelter M, Jacobson CE 4th, Wang X, Gordon CW Jr, Zeilman P, Romrell J, Martin P, Ward H, Rodriguez RL, Foote KD. Cognition and mood in Parkinson's disease in subthalamic nucleus versus globus pallidus interna deep brain stimulation: the COMPARE trial. Ann Neurol. 2009 May;65(5):586-95. doi: 10.1002/ana.21596. PMID: 19288469; PMCID: PMC2692580.

10. Starr PA, Vitek JL, DeLong M, Bakay RA. Magnetic resonance imaging-based stereotactic localization of the globus pallidus and subthalamic nucleus. Neurosurgery. 1999 Feb;44(2):303-13; discussion 313-4. doi: 10.1097/00006123-199902000-00031. PMID: 9932883.

11. Esselink RA, de Bie RM, de Haan RJ, Lenders MW, Nijssen PC, Staal MJ, Smeding HM, Schuurman PR, Bosch DA, Speelman JD. Unilateral pallidotomy versus bilateral subthalamic nucleus stimulation in PD: a randomized trial. Neurology. 2004 Jan 27;62(2):201-7. doi: 10.1212/01.wnl.0000103235.12621.c3. PMID: 14745054.

12. Herzog J, Fietzek U, Hamel W, Morsnowski A, Steigerwald F, Schrader B, Weinert D, Pfister G, Müller D, Mehdorn HM, Deuschl G, Volkmann J. Most effective stimulation site in subthalamic deep brain stimulation for Parkinson's disease. Mov Disord. 2004 Sep;19(9):1050-4. doi: 10.1002/mds.20056. PMID: 15372594.

13. Haberler C, Alesch F, Mazal PR, Pilz P, Jellinger K, Pinter MM, Hainfellner JA, Budka H. No tissue damage by chronic deep brain stimulation in Parkinson's disease. Ann Neurol. 2000 Sep;48(3):372-6. PMID: 10976644.

14. Krack P, Batir A, Van Blercom N, Chabardes S, Fraix V, Ardouin C, Koudsie A, Limousin PD, Benazzouz A, LeBas JF, Benabid AL, Pollak P. Five-year follow-up of bilateral stimulation of the subthalamic nucleus in advanced Parkinson's disease. N Engl J Med. 2003 Nov 13;349(20):1925-34. doi: 10.1056/NEJMoa035275. PMID: 14614167.

15. Krack P, Limousin P, Benabid AL, Pollak P. Chronic stimulation of subthalamic nucleus improves levodopa-induced dyskinesias in Parkinson's disease. The Lancet. 1997 Dec 6;350(9092):1676. doi: 10.1016/S0140-6736(05)64273-0.

16. Volkmann J, Allert N, Voges J, Sturm V, Schnitzler A, Freund HJ. Long-term results of bilateral pallidal stimulation in Parkinson's disease. Ann Neurol. 2004 Jun;55(6):871-5. doi: 10.1002/ana.20091. PMID: 15174022.

17. Okun MS, Green J, Saben R, Gross R, Foote KD, Vitek JL. Mood changes with deep brain stimulation of STN and GPi: results of a pilot study. J Neurol Neurosurg Psychiatry. 2003 Nov;74(11):1584-6. doi: 10.1136/jnnp.74.11.1584. PMID: 14617726; PMCID: PMC1738229.

18. Funkiewiez A, Ardouin C, Caputo E, Krack P, Fraix V, Klinger H, Chabardes S, Foote K, Benabid AL, Pollak P. Long term effects of bilateral subthalamic nucleus stimulation on cognitive function, mood, and behaviour in Parkinson's disease. J Neurol Neurosurg Psychiatry. 2004 Jun;75(6):834-9. doi: 10.1136/jnnp.2002.009803. PMID: 15145995; PMCID: PMC1739075.

19. Soulas T, Gurruchaga JM, Palfi S, Cesaro P, Nguyen JP, Fénelon G. Attempted and completed suicides after subthalamic nucleus stimulation for Parkinson's disease. J Neurol Neurosurg Psychiatry. 2008 Aug;79 (8):952-4. doi: 10.1136/jnnp.2007.130583. Epub 2008 Apr 10. PMID: 18403439.

20. Schüpbach M, Gargiulo M, Welter ML, Mallet L, Béhar C, Houeto JL, Maltête D, Mesnage V, Agid Y. Neurosurgery in Parkinson disease: a distressed mind in a repaired body? Neurology. 2006 Jun 27;66 (12):1811-6. doi: 10.1212/01.wnl.0000234880.51322.16. PMID: 16801642.

"Blinding of Neurosurgical Trials & Deep Brain Stimulation "

Navaneeth Natarajan
MBBS Medicine

In a 2012 paper, neurosurgery was awarded the honour, or rather dishonour, for having the fewest Randomised Control Trials (RCTs) in scientific literature compared to any other medical speciality[1]. A major factor for this poor statistic can be attributed to the heightened challenges neurosurgical trials face when attemtping to blind its participants and/or administers of the intervention placed. However, studies involving Deep Brain Stimulation (DBS) somehow beat all the odds and produced thorough RCTs, despite these hardships. This therefore begs the question: "how?"

"RCTs are the gold standard of all clinical trials". This is by far the principle most lecturers drill into any research student's brain. For those unfamiliar to RCTs, they are a type of clinical trial where a new treatment or procedure is compared to the standard methods currently used in clinical settings, in order to observe which approach is superior. Individuals are randomly split into control and intervention groups, with each having a similar demographic (for example being of similar age, sex, race, etc.) [2] This aspect of randomisation is achieved via the process of "blinding", where participants within a trial are unaware of which cohort they are a part of (the control or intervention) in order to reduce performance bias[3]. A "double-blinded" trial goes the extra step to reduce unwanted bias, as even those performing the interventional procedure within the trial do not know if they are serving participants of the cohort or the interventional group. It is this aspect of randomisation that allows RCTs to get the "gold standard" seal of approval, but is the most

difficult to achieve in neurosurgical studies.

Blinding in surgical trials is quite difficult to achieve – both from a practical and ethical point of view. Unlike pharmaceutical trials, where the interventional medication and the placebo drug can be given in visually identical pills, devices such a as neurostimulators (the device inserted to aid DBS) do not have the privilege of "camouflage" for obvious reasons. This leads to RCTs as a whole being abandoned by many surgical trials. A 1995 paper only serves to bolster this, as it highlighted that only 38.8% of treatment evaluation questions concerning surgical operations could feasibly be answered using a RCT[4]. Furthermore, the blinding of surgeons can be impractical most of the time. Surgeons ought to know who is in the intervention group in order to make the appropriate incisions needed to administer the right chemical agent or device to participants. One could suggest that all the participants, regardless of their assigned group, should be given the same incisions/procedure, with only the interventional cohort actually receiving treatment to produce at least a single-blinded investigation. This technique, known as a "sham surgery", is quite controversial due to its ethically dubious nature, as it entails performing invasive surgery on humans with the deliberate intent of not treating some of them[5]. With all of this damming evidence against blinding in surgery, it can be easy to become pessimistic and complacent that neurosurgical trials and RCTs can never coexist. However, DBS studies proved otherwise through the process of "staggered stimulation".

The biggest advantage of a neurostimulator is its ability to turn "on" or "off" fairly easily. Therefore, in a DBS trial, whilst all participants (irrespective of their group allocation) will undergo surgery to implant a neurostimulator, not all of them will be turned on immediately[6]. Only participants within the interventional cohort will have their device turned on once it has been programmed some weeks after surgery. Hence, they are named the "early stimulation" group. The control group, who also have neurotransmitters implanted, are known as the "late stimulation" group as their neurostimulators remain switched off during the initial programming phase. However, these too will be switched on after roughly 25 weeks. Therefore, by the end of the trial, all participants, regardless of their group, will have their neurostimulators switched on (Fig. 1). This allows for a double-blinded RCT to occur as neither the participants, nor the investigators, will know who has been randomly allocated to have their neurotransmitter switched on or off by the programmer during the initial programming phase. It also circumvents the dubious ethics of "sham" surgeries as by the end of the trial, all participants have a switched on neurostimulator, making the surgeries morally legitimate.

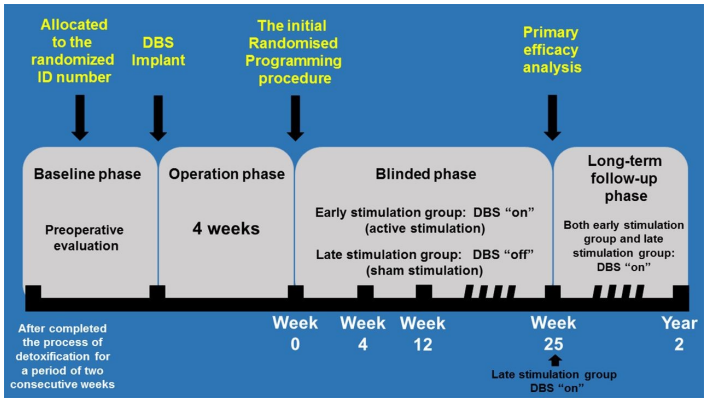


Fig.1 Blinding methodology in deep brain stimulation trials

While this particular method of blinding certainly cannot absolve the problems facing every neurosurgical trial, it certainly highlights that there are solutions that can allow surgical trials to be both at an optimum clinical standard, whilst also not actively endangering anyone involved. For example, while surgeons may need to ascertain whom they are performing a procedure on, other members of staff involved in the trial such as nurses or psychiatrists do not need to know which group a patient is in. Therefore, blinding these people can allow at least some bias to be reduced. Further research could also be done on whether a "sham" surgery needs to be performed in order for a placebo to be effective. Would merely telling the participants they had surgery when in reality they were just under a sedative in hospital with no procedure performed on them produce the same effect? This could possibly allow an ethical way of blinding participants at least.

In the end, as with any scientific problem, what is required is a little ingenuity and a lot of thinking. And with time, improvements can be made within the designing of neurological trials if effort and research is put into finding a solution to its problems. For after all, the saying still stands – when there is a will, there will be a way.

References

1. Levels of evidence in the neurosurgical literature: more tribulations than trials. Yarascavitch, Blake A, et al. 6, 2012, Neurosurgery, Vol. 71, pp. 1131-1138.

2. Medical Research Council. What is a randomised clinical trial? [Online] 2018. [Cited: 14 January 2020.] https://www.ctu.mrc.ac.uk/patients-public/about-clinical-trials/what-is-a-randomised-clinical-trial/#:~:text=What%20is%20a%20randomised%20clinical%20trial%3F%201%20Randomised,6%20For%20more%20information%20about%20clinical%20trials.%20.

3. Blinding: an essential component in decreasing risk of bias. Forbes, Dr. Dorothy. 3, 2013, Evidence Based Nursing, Vol. 16, p. 70.

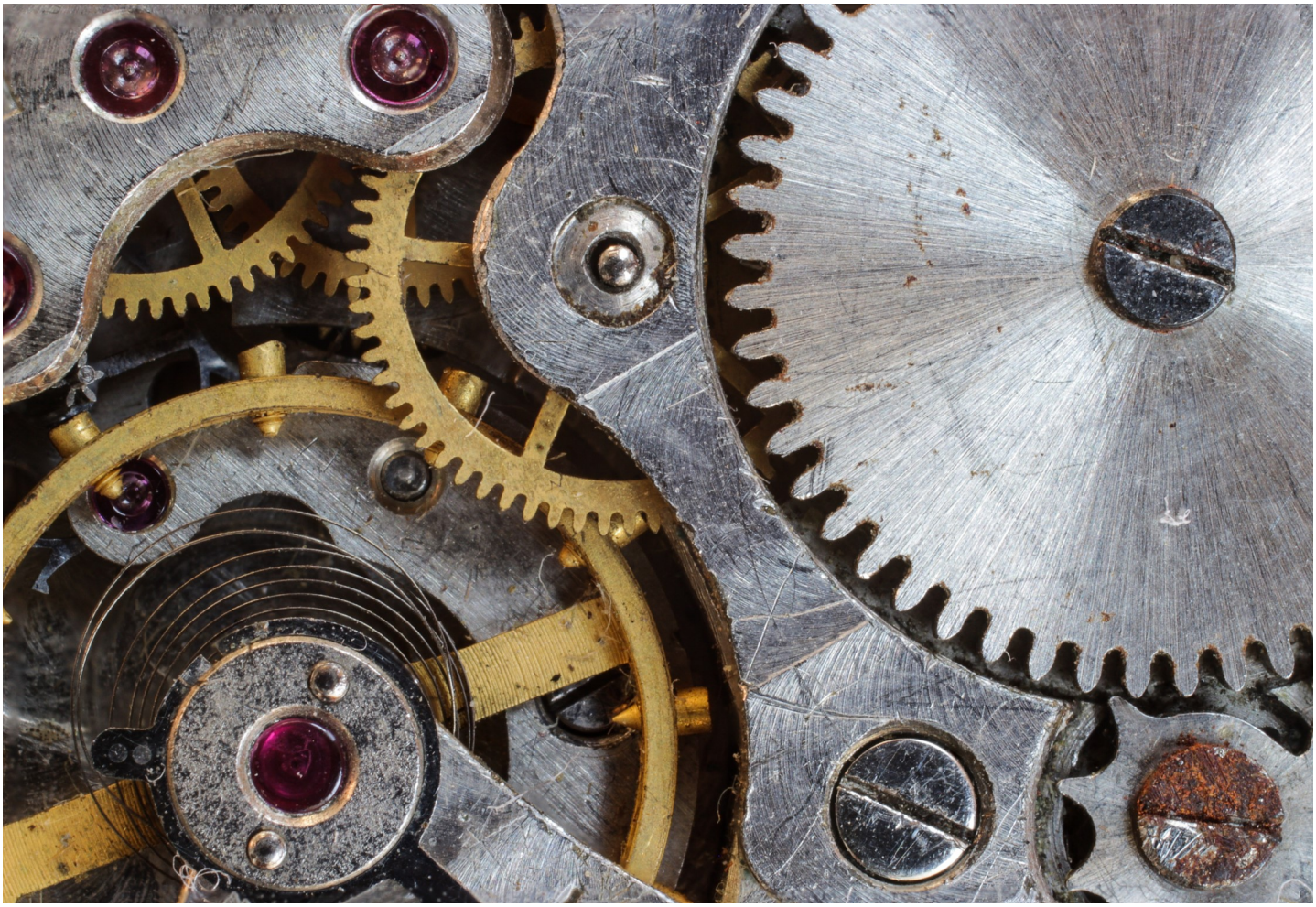
4. Should we be performing more randomized controlled trials evaluating surgical operations? Solomon, Michael J and McLeod, Robin S. 3, 1995, Surgery, Vol. 118, pp. 459-467.

5. Kwon, Rachel J. Sham surgery: Is it inherently unethical? [Online] 2013. [Cited: 16 January 2020.] https://www.ideal-collaboration.net/2013/06/845/.

6. Clinical evaluation of deep brain stimulation of nucleus accumbens/ anterior limb of internal capsule for opiiod relapse prevention: protocol of a multicentre, prospective and double-blinded study. Qu, Liang, et al. 2, 2019, BMJ Open, Vol. 9.

2

Brain Computer Interfaces



“Transhumanism: Transforming Mind into Machine”

What a piece of work is a man! How noble in reason!

How infinite in faculty! In form and moving how

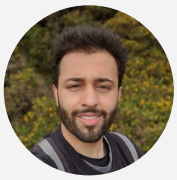
express and admirable! In action how like an angel!

In apprehension how like a god! The beauty of the

world! The paragon of animals! And yet, to me,

what is this quintessence of dust?

— Hamlet, Act 2 Scene 2



Hamaad Khan
BSc Neuroscience

The human brain remains a remarkable piece of biology. Everything we know about the world is provided to us by an organ that has itself never seen that world. Yet, it just takes 1.6kg of the stuff to conjure the rich and visceral experience of our every waking moment. And though new discoveries are teaching us more than we ever know, the advent of brain computer interfaces is reaching deep into the hinterland of the mind and transforming the very idea of what it means to be human.

Brain computer interfaces, or BCI for short, wire up the brain to a computer, reading the pinpricks of electrical currents pulsing across our axons at 250 mph. Capturing thoughts in sharp peaks and troughs is far from revolutionary however — recording the electrical activity of the brain was first done in 1924 [1]. Though machines have long been able to read the human brain, what's new is their ability to interpret it. Aided by sophisticated algorithms, computers can now translate a flurry of electrical readings into physical actions.

We now have BCIs that use neural signals to control robotic arms [2], draw faces we think about [3], type and move cursors [4], and even restore the sense of touch [5]. What once was carried out dutifully within our soft organic bodies, is now being performed by machines outside the membrane of our biology. It seems that the mind, and all that it commands, can be extended beyond its gelatinous strands of fat and protein, and hardened into steely wires carrying binary code for machines. This excites transhumanists, who have long yearned to be liberated from the wear and tear of human biology.

The truth is, we are in a constant state of bodily loss from the moment we are born into this world. Our youth, with all its elasticity, simply does a good job springing back from the losses. We lose teeth for stronger ones to grow in. Old cells slough off to make way for newer ones. Hair falls out only to grow back again. But eventually this all stops. The sagginess of time contours our skin with faint grooves, our face etched with lines. Our sunken flesh drops. Hair only falls. Teeth and bone only break. Dementia settles in. Cancer grows out. Time eventually exposes us for the fragile beings that we are — feeble, bleeding and marked for death.

Frustrated by this pitiful human condition, transhumanists seek a stronger shape and form of existence. By inscribing intelligence onto inorganic matter, there is hope to eradicate death; replacing flesh and blood for files and filaments. Successes of BCIs prove that, at least in a limited capacity, this can happen: our minds can be carried by machine.

So is future humanity destined to become machines? Well, while some human actions can be computed, general intelligence seems to be a function of organic life, not of inorganic tools. It's a writer's mind, not his typewriter, that marks his intelligence. Modern BCIs are just the same. As inorganic tools, they simply mime out the intelligence projected onto them. So long as they run on human-written code, machines will only reflect the mind's intelligence.

And though it remains to be seen if promises of future technology—with better efficiency and better storage—can ever capture the essence of ourselves in forms of pixels, wires and transistors, BCIs still have a lot to offer our earthly bodies.

Unlike transhumanism, which sees life as a disease from which we all suffer, the clinical application of BCIs is much less cynical. In recovering lost biological functions, like sight and hearing, BCIs seek the restoration of quality in life. Far from a dismal disease from which we all must escape, life *is* the cure. It allows us to live well again, 'noble in reason' and 'infinite in faculty'.

References

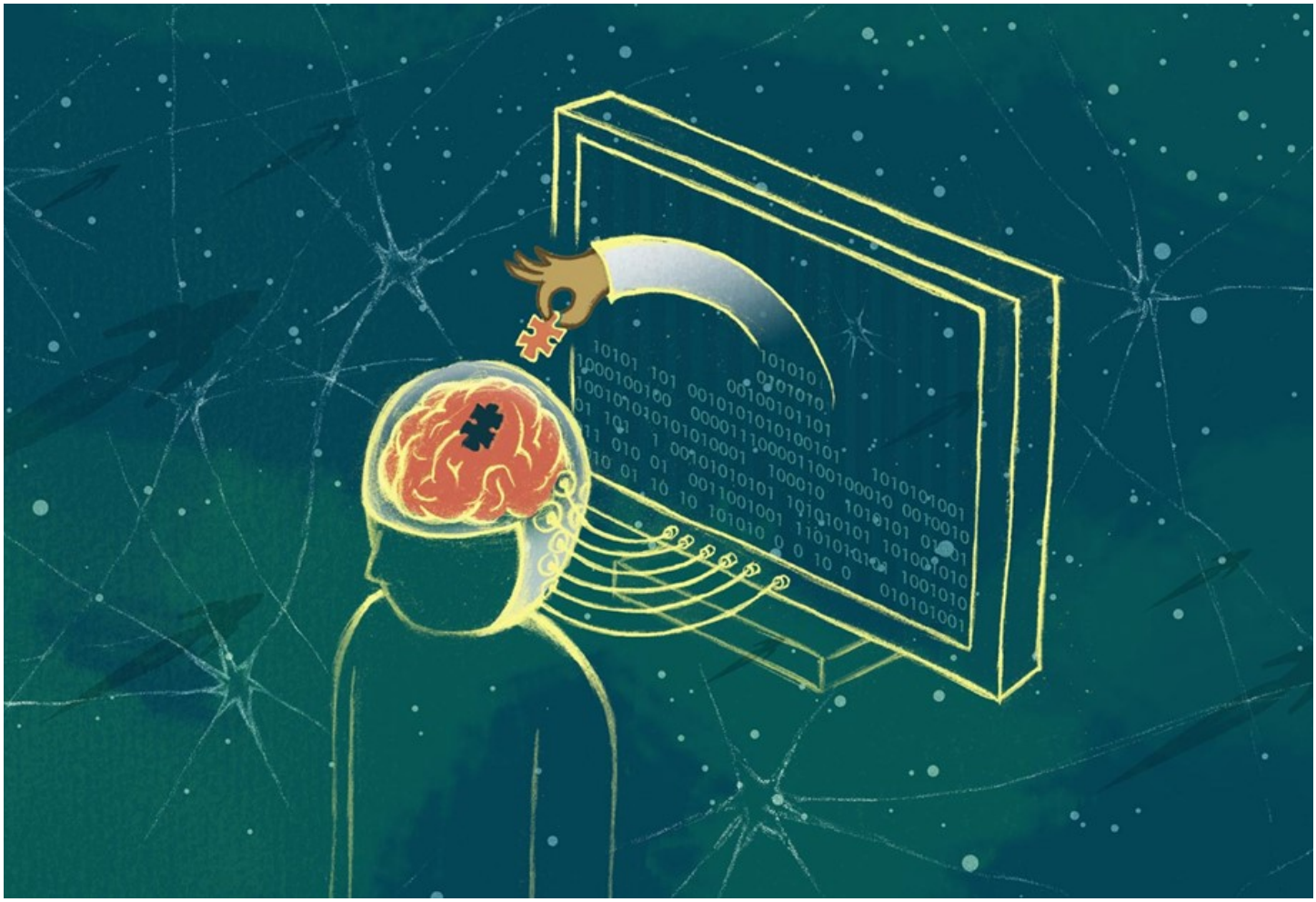
1. Haas L. Hans Berger (1873-1941), Richard Caton (1842-1926), and electroencephalography. Journal of Neurology, Neurosurgery & Psychiatry. 2003;74 (1):9-9

2. Casey A, Azhar H, Grzes M, Sakel M. BCI controlled robotic arm as assistance to the rehabilitation of neurologically disabled patients. Disability and Rehabilitation: Assistive Technology. 2019;:1-13.

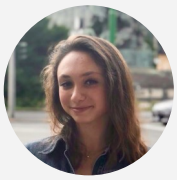
3. Kangassalo L, Spapé M, Ruotsalo T. Neuroadaptive modelling for generating images matching perceptual categories. Scientific Reports. 2020;10(1)

4. Nuyujukian P, Albites Sanabria J, Saab J, Pandarinath C, Jarosiewicz B, Blabe C et al. Cortical control of a tablet computer by people with paralysis. PLOS ONE. 2018;13(11):e0204566

5. Ganzer P, Colachis S, Schwemmer M, Friedenberg D, Dunlap C, Swiftney C et al. Restoring the Sense of Touch Using a Sensorimotor Demultiplexing Neural Interface. Cell. 2020;181(4):763-773.e12.



“Cochlear Implants & Auditory Prosthesis”



Carlotta Barelli
MSci Neuroscience

Hearing is not only a very useful tool to collect an incredibly vast and varied source of information about the world around us, but also often a very enjoyable activity. We are indeed very fortunate to have ears and, when they work as they should, they allow us to distinguish thousands of natural and artificial sounds effortlessly, as well as listen to music, communicate with other people and perhaps warn us that a car is crossing the road whilst we are in the middle of it.

Essentially, sound is pressure wave which propagates through the air and eventually reaches our ears. What is the most compelling about our auditory system is that long before we are consciously aware of the sound we are attending to, our brains have already extracted an enormous amount of information about these pressure waves, including the frequency or pitch of sound, its amplitude or loudness, its spatial localisation and perhaps even its source.

Now you may wonder, how sound as a physical phenomenon becomes sound as perception? The neurobiological process underlying this is sensory transduction, which is essentially the transformation of the mechanical energy contained in that pressure wave into electrical energy or neural activity, which will propagate from our peripheral sensory organs of sound, our ears, up towards our auditory brains.

As a sound wave hits our external ear, it enters the ear canal and pushes against the eardrum, which separates our external ear from our middle ear. The middle ear has the fundamental job of transmitting tiny sounds from the air-filled external ear to the cochlea, which sits in our inner ear. It is essential that

sound vibrations get amplified along their way to the cochlea and this is achieved via the relay along the chain of three small bones or ossicles in the middle ear, known as the malleus, the incus and the stapes. Vibrations of the stapes send fluid waves through the spiral-shaped cochlea, which is a busy little world of its own.

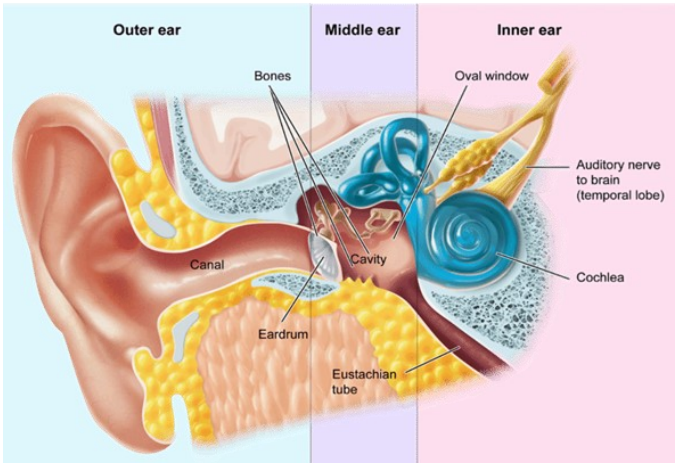


Fig.1: Major anatomical components of the mammalian Outer, Middle, and Inner Ear

The cochlea is filled with fluid surrounding some 10,000 to 15,000 tiny hair cells, which beautifully sway in response to the fluid-waves generated by the three ossicles. Inner hair cells (IHCs) are indeed the protagonists of sensory transduction as their stretching and bending results in the release of chemical neurotransmitters that activate the auditory fibres of the cochlear nerve, sending tiny electrical currents to the auditory brain. I must admit that I consider the cochlea as one of the most fascinating structures within our body as it hosts a so called "tonotopic map" along its snail-like arrangement.

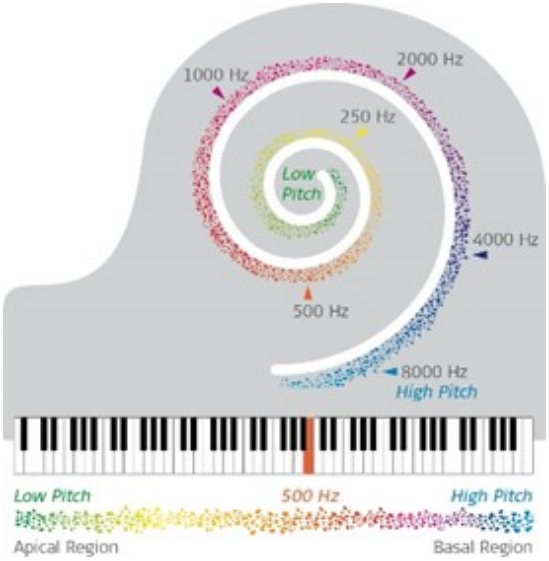


Fig.2: Tonotopic map in the spiral-shaped cochlea

Tonotopy refers to the spatial arrangement of where sounds of different frequencies are processed in the nervous system. Indeed, different regions of the basilar membrane in the organ of Corti, the sound-sensitive portion of the cochlea, vibrate at different frequencies of sound due to variations in thickness and width along the length of the membrane. Nerves that transmit information from different regions of the basilar membrane therefore encode frequency tonotopically.

The Inner Ear is also home to IHCs' close cousins: Outer Hair Cells (OHCs). OHCs have the fundamental job of mechanically amplifying the vibrations produced by the incoming sound. They do so by stretching and contracting rhythmically in response to sound. In his book "*Making Sense of Sound",* Dr. Schnupp rightly says that at parties, there are two types of people: those who enjoy listening to conversation, and those who prefer to dance. With hair cells it is similar: IHCs listen and talk to other nerve cells, while OHCs literally dance by moving in tune to the rhythm of the music.

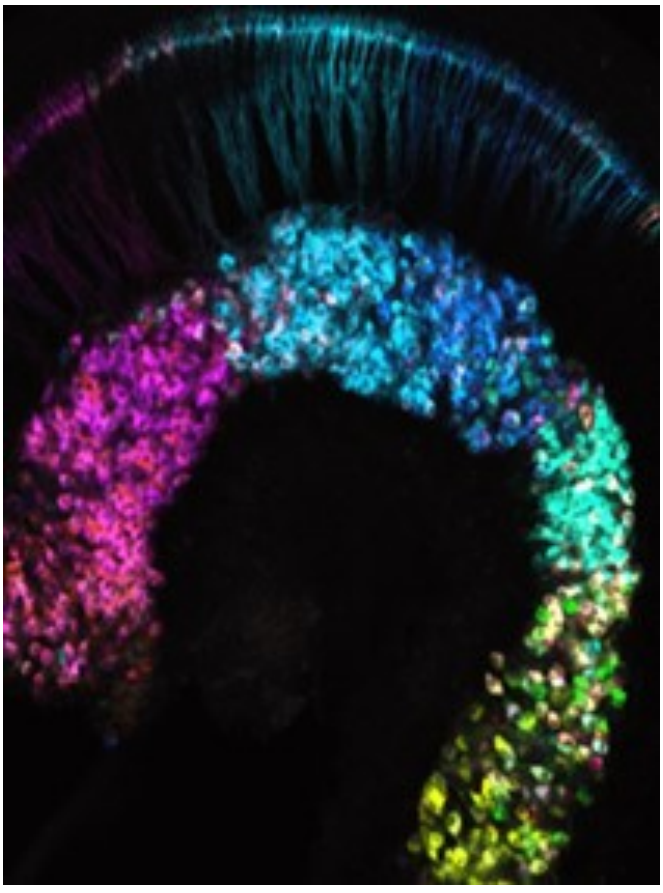


Fig.3: Spontaneous correlated firing in the developing mouse cochlea (from Wang and Babola, 2021)

Hearing research is one the great science-tech success stories of the last 100 years. New discoveries about the nature of the sound and the working of the ear have gone hand in hand with technological advancements in the telecommunications, media and, most importantly, in clinical applications designed for patients with hearing impairment.

The downside of the precision and subtlety by which the inner ear and middle ear work is that they are also extremely delicate and fragile structures. Indeed, they are very easily damaged by disease, noise trauma or other injuries and, although hard to accept, sooner or later, hearing will start go wrong in each one of us. The most common cause of hearing loss is damage to cochlear hair cells and, in particular to outer hair cells, which have the fundamental job of amplifying the sound wave travelling along the spiral-shaped cochlea. If you think about it for a moment, the consequences of hearing impairment can be tragic: social interactions become extremely challenging, the joy of listening to music soon disappears and stimulating conversation is nearly impossible. However, technological advancements in the recent years have reshaped the lives of hundreds of thousands of patients; cochlear implants have allowed profoundly deaf people to pick up the phone and call a friend.

The principle underlying hearing aid devices is fairly simple: as hearing damage stems from decreased or lack of amplification of the sound wave in the inner or middle ear, artificially driven amplification of the incoming vibrations can be highly beneficial. Already in the 1800s, "ear trumpets" were designed and aimed at amplifying the sound entering in the ear canal by purely mechanical means. They were relatively widely used despite the clear "cosmetic side effects", which led King John VI of Portugal to construct a throne in which an ear trumpet was worked into one of the arm rests, disguised as a fierce lion head (figure 4). The ear trumpet was then connected to the King's ear via a tube and subjects wishing to talk to the King were asked to kneel and speak into the lion's mouth.

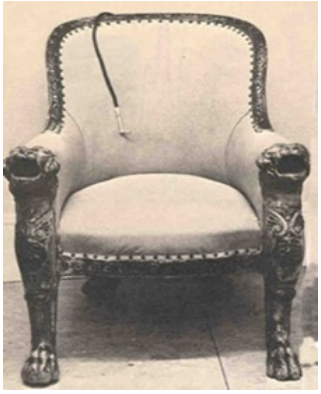


Fig.4: King John VI of Portugal's throne with disguised ear trumpets

Technology has now moved far from that and nowadays hearing aids are much more portable and they are often entirely concealed behind the pinna or the ear canal. Moreover, not all sensorineural hearing impairments are the same, highlighting the need for matching and adapting the artificial amplification provided by the device with the specific deficits of the user. It is often the case that sensorineural hearing loss affects mostly high-frequency sounds and, thus, if the patient is supplied by a device which indiscriminately amplifies all frequencies, it will overamplify the patient's low frequency hearing, concealing the high frequencies which were aimed to be amplified. Accordingly, modern electronic hearing aids offer nonlinear amplification and "dynamic gain control", adapting to the patients deficits and needs.

Cochlear implants are the most widely provided hearing aid devices to the many patients who are severely deaf due to extensive damage to their hair cells. At present, regenerative medicine and stem cell research have not yet achieved a method to regenerate and repair damaged or lost sensory hair cells in the mammalian inner ear. Even after years of profound deafness, the majority of hearing impaired patients still retain many thousands of auditory nerve fibres in perfect health, waiting for sensory input to come in. Surprisingly, most patients also have the majority of their IHCs in good condition while their OHCs are extensively damaged, failing to provide that mechanical amplification which is fundamental for sensory transduction. Therefore, the way cochlear implants work is by skipping one step along the line of

"normal sensory transduction" and directly stimulating the healthy nerve fibres with pulses of electrical activity. Having in mind the perfectonotopic organisation of the cochlea, it should come with no surprise to you that the electrical stimulation of the auditory nerve fibres by the wires of the cochlear implant must be extremely targeted and specific. To achieve this, the extracellular electrodes must be placed in close proximity to the auditory fibres and, thus they are surgically inserted into the canals of the cochlea. Practically, the intracochlear electrode is threaded into the cochlea and it receives electrical signal from a receiver device, which is implanted under the scalp, on the surface of the skull, behind to the outer ear. The receiver device receives its signal and electrical energy from a headpiece radio transmitter, which is itself connected to a "speech processor" placed behind the external ear. This speech processor collects sounds from the environment through a microscope and encodes them into appropriate electrical signals which are sent to the subcutaneous receiver.

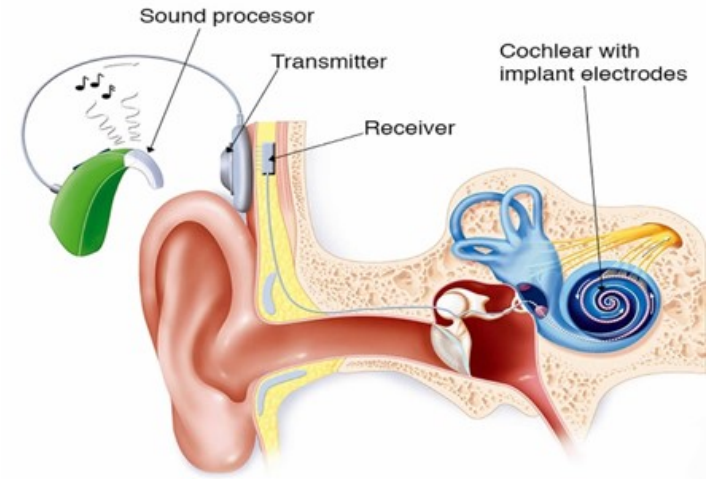


Fig.5: Diagram of a modern cochlear implant

The sad news is that cochlear implants are designed to process speech, which is a much simpler auditory signal compared with music. Prudence Garcia-Renart, a musician who gave up playing the piano a few years ago following several years of cochlear implant, says "I've pretty much given up listening to music and being able to enjoy it. I've had the implant for 15 years now and it has done so much for me. I can now use a phone, I recognize people's voices, I go to films, but music is awful." For now, it is unrealistic to expect people with an implant to process the complexity of a symphony. Therefore, technology has changed route and members of Columbia's Cochlear Implant Music Engineering Group are trying to reengineer and simplify music to be more enjoyable for listeners with cochlear implants. The group is testing different arrangements of musical compositions to learn which parts of the music are most important for listener enjoyment. Their aim is to generate a software which will be able to take an original piece of music and reconfigure it for cochlear implantees.

I want to leave you with a last fact which encapsulates the intriguing, complex and perhaps frightful relationship between neuroscience and technology. Our nervous system is extremely plastic and susceptible to experience-dependent changes. Indeed, following several years of deafness, the auditory cortex can be taken over by other sensory modalities and this process can be reversed by implanting hearing aid devices, which over time induce cortical forms of plasticity especially in young children. Nowadays, technology can very easily interfere, re-shape and control neural activity. Of course, this allows for extremely powerful therapeutic strategies and for the brain to adapt to these life-changing protheses including cochlear implants. At the same time, this raises a note of caution and an important reminder about the susceptibility, naivety and sensitivity of our brains.

Further Reading

Satoh, M., Evers, S., Furuya, S. and Ono, K., 2015. Music in the Brain: From Listening to Playing. *Behavioural Neurology*, 2015, pp.1-2.

Schnupp, J., King, A. and Nelken, I., 2012. *Auditory Neuroscience*. Cambridge: The MIT Press.

Vlajkovic, S., Thorne, P., Rajan, R. and Gale, J., 2015. Preventing Hearing Loss and Restoring Hearing: A New Outlook. *BioMed Research International*, 2015, pp.1-2.

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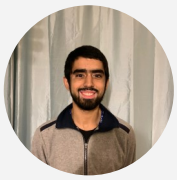
“Brain Computer Interfaces for the use of Prosthetics”



Ibraheem Bin-Suhayl
BSc Neuroscience

Neurotechnology has been a rapidly developing field that can allow for recording of brain activity and stimulating specific areas of the brain using Brain Computer Interfaces (BCI). This technology has many clinical applications, one being in use alongside prosthetics to treat certain disorders such as paraplegia. Paraplegia affects many people and it greatly impacts quality of life. While paraplegics often use prosthetics, these can be very simple.

For many years, there has been research into using BCI to provide a connection between prosthetic and the brain of the patient. Ideally, this would allow patients to be able to naturally control the prosthetic arm using brain activity, and also receive information from artificial sensors on the prosthetic to produce a natural perception of touch.

This research has been carried out for multiple years and the first BCI prosthetics were those that only allowed patients to control the prosthetic arm using their brain activity, without sending information back to the brain[1]. But in a breakthrough study in 2016 by Flesher et al. of Pittsburgh university, a patient was connected to a prosthetic arm that could transfer information both ways[2]. This meant that the prosthetic could both be controlled by brain activity as well as produce the perception of touch in the patient. Such prosthetics could greatly improve quality of life in patients.

Paraplegia is not the only area where BCI prosthetics can be used. There has been increasing research in treating blindness by using BCI to bypass areas of damage. This concept was demonstrated

where a microchip was implanted to the retina which would stimulate the optic nerve of a blind woman which partially restored sight[3]. However, this technique would not help those whose blindness was caused by damage along the visual pathway. This problem could be dealt by using a BCI to directly stimulate the visual cortex which has been accomplished. In 2020, Fernandez demonstrated the partial restoration of sight in a blind patient after implantation of an electrode array onto the visual cortx[4].

For the future, there are multiple issues that the field will have to overcome for these BCI prosthetics to become more commonplace for clinical treatment.

One such issue is with how the commonly-used electrode arrays are very invasive, and as such, come with many risks including the possibility of infections and the development of scar tissue which can also lead to a drop in effectiveness of the array. There is a fair amount of research into developing BCI that is less invasive or more compatible with the brain and ergo carry less risks. These include the 'Neural Dust' developed by a Seo et al. at UC Berkeley[5], a new electrode 'injection' technique and robot developed by Neuralink[6], and non-invasive stimulation methods such as Temporal Interference[7].

Another area for future BCI research is in further mapping of brain areas and decoding their patterns of activity. For a BCI to recreate a certain sensation and perception, it needs to 'know' what specific areas to simulate to create the relevant pattern of activity. While the somatosensory cortex is relatively well-understood with its homunculus map, there are many other areas of the brain that are less well mapped out such as the visual cortex. One notable study into mapping and decoding the visual cortex was by Nishimoto et al. of UC Berkeley in 2011 where they attempted to recreate videos from visual cortex activity using a machine learning algorithm[8].

In conclusion, BCIs are a promising 'upgrade' for multiple types of prosthetics, including tactile and visual prosthesis, and can greatly increase the quality of life for many patients. However, there are many issues and areas that the technology needs to overcome and improve in, such as compatibility and decoding of brain activity. But BCI is becoming more prominent in research and there are many companies, such as Neuralink, interested in this technology and its potential uses. Due to this increasing interest, research will soon overcome the limitations and advance the functionality of BCIs allowing them to be used much more for the clinical treatment of multiple disorders.

References

1. Collinger, J. L., Wodlinger, B., Downey, J. E., Wang, W., Tyler-Kabara, E. C., Weber, D. J., McMorland, A. J., Velliste, M., Boninger, M. L., & Schwartz, A. B. (2013). High-performance neuroprosthetic control by an individual with tetraplegia. Lancet (London, England), 381(9866), 557–564. https://doi.org/10.1016/S0140-6736(12)61816-9

2. Flesher, S. N., Collinger, J. L., Foldes, S. T., Weiss, J. M., Downey, J. E., Tyler-Kabara, E. C., . . . Gaunt, R. A. (2016). Intracortical microstimulation of human somatosensory cortex. Science Translational Medicine, 8(361), 361ra141. doi:10.1126/scitranslmed.aaf8083

3. British woman with 'bionic eye' speaks of joy after reading clock for first time in years. (2016). Retrieved from http://www.theguardian.com/society/2016/jan/05/woman-bionic-eye-joy-reading-clock-rhian-lewis

4. Juskalian, R. (2020). A new implant for blind people jacks directly into the brain. Retrieved from https://www.technologyreview.com/2020/02/06/844908/a-new-implant-for-blind-people-jacks-directly-into-the-brain/

5. Seo, D., Neely, R. M., Shen, K., Singhal, U., Alon, E., Rabaey, J. M., . . . Maharbiz, M. M. (2016). Wireless recording in the peripheral nervous system with ultrasonic neural dust. Neuron, 91(3), 529-539. doi:10.1016/j.neuron.2016.06.034

6. Musk, E., & ,. (2019). An integrated brain-machine interface platform with thousands of channels. bioRxiv, , 703801. doi:10.1101/703801

7. Grossman, N., Bono, D., Dedic, N., Kodandaramaiah, S. B., Rudenko, A., Suk, H., . . . Boyden, E. S. (2017). Noninvasive deep brain stimulation via temporally interfering electric fields. Cell, 169(6), 1029-1041.e16. doi:10.1016/j.cell.2017.05.024

8. Nishimoto, S., Vu, A., Naselaris, T., Benjamini, Y., Yu, B., & Gallant, J. (2011). Reconstructing visual experiences from brain activity evoked by natural movies. Current Biology, 21(19), 1641-1646. doi:10.1016/j.cub.2011.08.031

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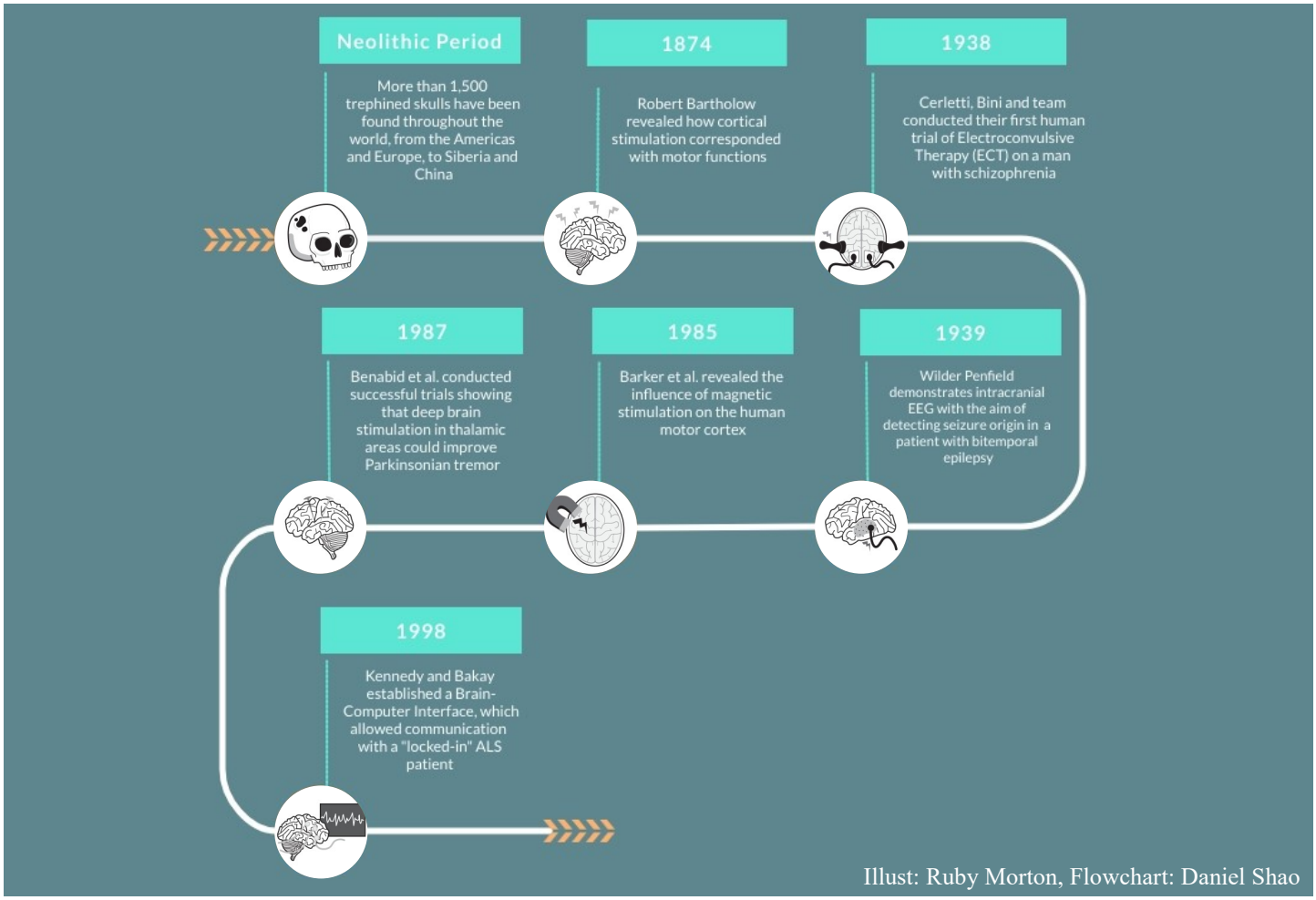
National Conference 2021



Illust: Ruby Morton, Flowchart: Daniel Shao

"Touching the Brain: A History"

Jubilent Amalendran
MBBS Medicine

In humankind's efforts to understand the brain, there have been numerous attempts to expose it to the naked eye, measure from within, and stimulate its matter. Unlike dogs, humans have caught our tail, and we have probed into it; yet we are far from completely knowing how it works. Nevertheless, with each attempt to touch the brain, we have come closer to a unified understanding, and there have indeed been clinical successes in this journey. We have progressed from mere conversation about the brain and crude anatomical dissection, to sophisticated interventions that not only explore but enhance peoples' lives. Let us take a whistle-stop tour through humanity chasing its tail and explore a few methods we have employed to touch the brain.

Most of us are familiar with Paul Broca for his discovery of Broca's area, a region in the frontal lobe associated with the motor components of speech generation. However, in his scientific career, the French physician published more papers on a different topic; he was a contributor to the era's plague of scientific racism (masquerading as 'physical anthropology'), but in 1867 an encounter with a pre-Columbian Peruvian trepanned skull generated a persistent interest that led to the discovery of much older, yet successful trepanations, and a lifetime of work attempting to explain how and why these trepanations were performed. Trepanation is the act of creating a hole in the skull (figure 1), exposing the *dura mater* within the intracranial cavity. Broca was a pioneer in suggesting that trepanation was performed deliberately and on living humans who often survived the procedure; previously, holes in dug-up skulls were merely assumed to be secondary to battle wounds or animal attacks. Modern archaeology demonstrates evidence of successful trepanation across a range of cultures and eras, suggesting that it was not purely a ritualistic practice limited to savage tribes with strange beliefs. In times with limited tools and

incorrect mechanistic understanding, trepanning nevertheless seems a rational solution to head injury or neurological signs; raised intracranial pressure often presents as throbbing headaches, so it doesn't seem that far-fetched that one would want to release 'stuff' from inside the skull. Indeed, trepanning (under a new name of craniotomy) is performed to manage certain types of extra axial haemorrhages even today, albeit with more grace (and in a sterile field). Overall, this primitive procedure is the first known attempt by humans at 'neurosurgery' and its ubiquity through time suggests that our earliest method of touching the brain was not a complete failure.

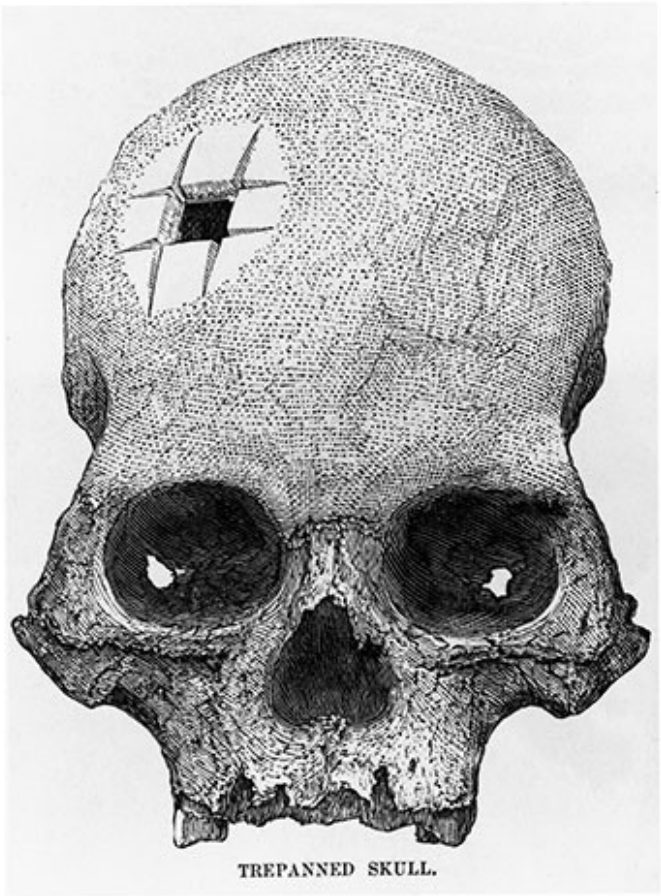


Fig.1: an illustration of the trepanned skull presented to Broca; note the scalloped edges surrounding the hole, suggesting methodological boring

However, we all know that mere physical touch is limited, and that the real language of our neurones is electrochemical. Early experiments by Luigi Galvani were seminal to this notion. In an era where electricity was the scientific fad, Galvani began his experiments with *fluido electrico* (electric fluid) and frogs' legs around 1770. Through rigorous experimentation (sparked by a serendipitous observation), he suggested that electricity could travel through the body and that frogs' muscles could be stimulated to contract by electricity – these, however, were not new findings. It was the idea that the muscles could contract without an external source of electricity and thus must have an inherent source of electricity, that were influential and set forth new thinking about how our nerves function. Galvani published his *Commentary on the Effects of Electricity on Muscular Motion* in 1791, coining the term 'animal electricity' for his ideas on how electricity activated muscles.

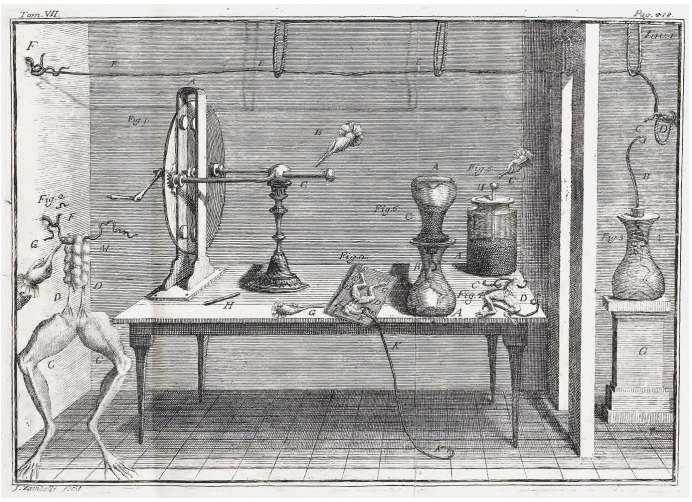


Fig.2: Galvani's complex apparatus as presented in his publication *Commentary on the Effects of Electricity on Muscular Motion*

Despite his enormous contribution, Galvani's experiments were unable to demonstrate how stimulating the (human) brain could cause movements in the muscles. This finding can be attributed to Robert Bartholow, who in 1874 performed experiments on the exposed cortex of Mary Rafferty, a consenting patient suffering from an expanding epithelioma that was corroding her skull. In his series of trials, he observed how when placing live electrodes on the left brain tissue, Rafferty's right limbs "made distinct muscular contractions" and vice versa when stimulating the right brain. However, the account continues: "In order to develop more decided reactions, the current was increased… [Rafferty] exhibited great distress, and she began to cry… the arm was agitated with clonic spasms; her eyes became fixed, with pupils widely dilated; lips were blue, and she frothed at the mouth…" A couple of days after the first experiments, Rafferty's condition declined, and she died. Bartholow himself accepted that he had caused his patient pain and accelerated her death. He subsequently apologised and stated that to repeat such experiments would be "the highest degree criminal."

Yet, 60 years on, an episode of déjà vu occurs. Inspired by work suggesting how induced seizures could relieve psychiatric symptoms, Italian psychiatrist Ugo Cerletti and his associate Lucio Bini trialled the first attempt of electroconvulsive therapy on a middle-aged man with schizophrenia. Electrodes were placed on the patient's temples and voltage was applied (the researchers had tested extensively on animals and themselves in preparation). The un-named man is reported to have jumped up on his bed, collapse with a loss of consciousness, then "sing at the top of his voice" before falling silent. Cerletti, knowing from his animal trials that the voltage had not been sufficient, deliberated repeating the shock with more volts. While the team discussed, the patient apparently pleaded, "not again, it will kill me!" But Cerletti did not concede and repeated the trial. The patient is reported to have experienced the "most typical epileptic fit," which then took a worrying turn: he stopped breathing, his apnoea exhibiting an "ashy paleness" and "cadaveric facial cyanosis" and seeming "painfully never ending…" It seemed like this mystery patient – a man found talking gibberish off a train from Milan, with no ticket, no identity – would suffer a similar fate to Mary Rafferty. However, to the relief of the experimenters, the man gradually awoke, "sat up of his own accord, looked about him calmly with a vague smile…" When asked what had happened to him, he replied, fluently for the first time since his discovery, "I don't know, perhaps I have been asleep." The man would undergo more treatments over two months and was discharged, symptomless for two years after which he was lost to follow-up. Cerletti and Bini presented their findings at the Medical Academy of Rome in May 1938, and over the next decade, electroconvulsive therapy (ECT) would become a widespread treatment for a range of psychiatric disorders. In the modern day, despite the stigma, generated from earlier misuses of the therapy and perpetuated by the media, ECT is indicated for treatment-resistant severe mental disorders and catatonia, and can be a life-saving treatment for patients in this group.

Whilst ECT involves extra-cranial stimulation of the brain, deep brain stimulation (DBS) is, as its name suggests, intra-cranial stimulation of subcortical matter. Although its modern clinical conception can be attributed to Alim Benabid and his team from Grenoble in 1987, early ideas of localising lesions and manipulating brain tissue therapeutically began in the 1930s, notably through the work of Wilder Penfield at the Montreal Neurological Institute. In 1939, he performed the first invasive EEG monitoring, where electrodes were placed onto the dura and helped identify the origin of epileptic seizures, thus guiding resection of the meningo-cerebral scar that seemingly caused the patient's seizures. (The extra-cranial EEG was discovered by Hans Berger in 1926.)

Although this specific case was unsuccessful – the seizures did not stop after surgery – Penfield and his colleagues' work at the institute inspired a multi-disciplinary approach to epilepsy management and highlighted the merit of intracranial electrical monitoring to reveal deeper understanding of seizure origin. These principles of localisation probably informed Benabid and team in their work on deep brain stimulation for patients with Parkinson's disease (PD). Initial trials on monkeys with an MPTP mutation (leading to the same destruction of the substantia nigra as is found in Parkinson's disease) revealed that stimulation of the subthalamic nucleus – a structure in the basal ganglia involved in movement pathways (that are deranged in parkinsonism) – could relieve some of the symptoms of disease. The subthalamic nucleus was then targeted in three patients with advanced PD, electrodes being placed bilaterally into their brains. Again, their motor symptoms significantly improved. A later study in 1998 showed similar improvements in motor symptoms and activities of daily living, in a larger cohort of PD patients, marking the start of a new era of DBS for Parkinson's disease. Although this technique has seen the greatest success against symptoms of PD, DBS has been trialled for other conditions including obsessive compulsive disorder and epilepsy. Since the initial trials in 1998, over 160,000 people have received DBS across the globe.

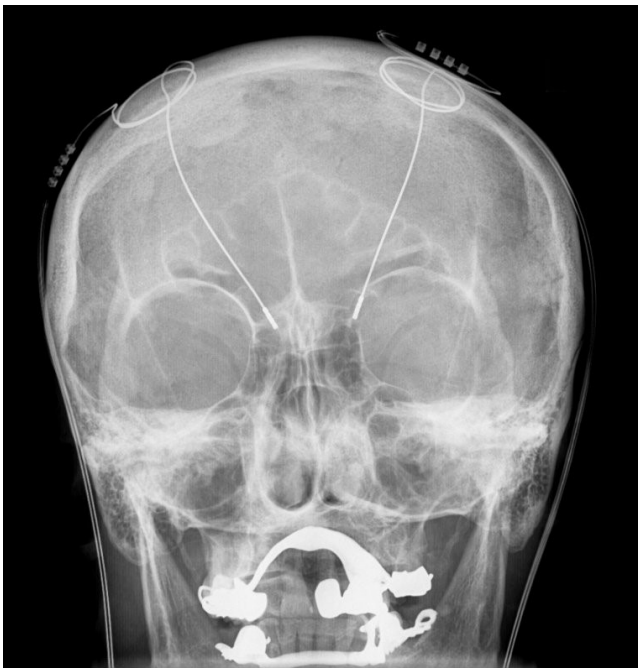


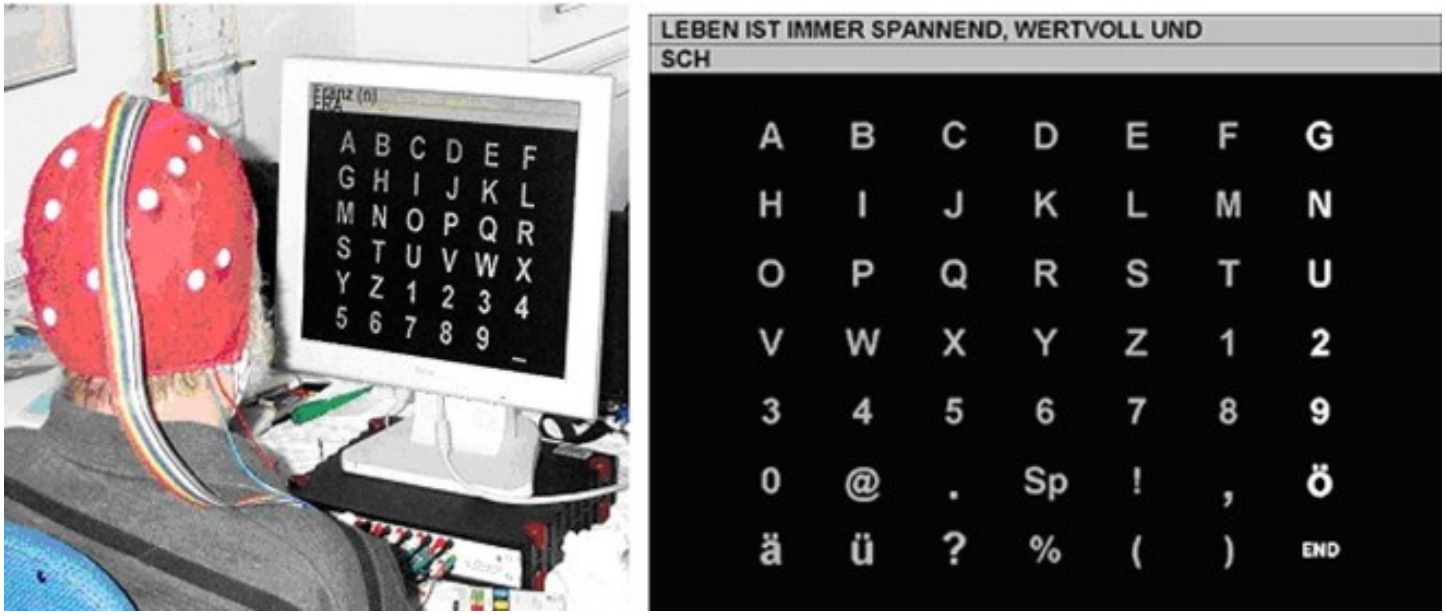
Fig.3: X-Ray image revealing bilateral DBS electrodes inserted in the deep subcortical matter

But for humans, simply putting electrodes into the brain, or recording its general electrical activity hasn't been enough. The idea of connecting machines to the mind has long existed in science fiction, but now it is a technology of reality. Brain computer interfaces (BCIs) – a term coined by Jacques Vidal in 1973 – are what blur the lines between imagination and invention. The general idea of BCIs is to bypass the physical link between our brains and machines, that is, to overcome the 'bandwidth' limitations of the body. The implications of such technologies are extensive and beyond the scope of this brief account, yet, from a clinical point of view, the major potential of BCIs is to alleviate the lives of those suffering from neuromuscular disorders that disable their muscles but preserve their brain. One of the first successes in this domain was in 1998, when Kennedy and Bakay were able to develop a communication link between a patient with amylotrophic lateral sclerosis, a disorder in which their motor neurones slowly lose function over time, leading to a state known as locked-in syndrome. Weeks after electrodes were implanted at her cortex, the patient was able to excite either an 'ON' or 'OFF' signal at the electrodes, using thought alone. Though only connected to a basic link that gave a binary signal, this was the first step, showing that brain activity could be quantified in live time.

Another BCI that has been used for patients with locked-in syndrome is the P300 system for spelling (figure 4). This system harnesses a normal frontal-parietal lobe relationship that produces an EEG waveform roughly 300ms after an unexpected stimulus appears mixed in with expected stimuli. This waveform is known as the event-related potential, that occurs consistently in all people, enabling it to be used reliably in patients. Imagine you are at a traffic light that is red, but you are keenly focussed on the (currently blank) green light. As soon as the light flashes green, your brain evokes this event-related potential. Similarly, patients who are unable to type can instead focus on the letter they want to spell on a grid of flashing letters, and as soon as the desired letter flashes, their event-related potential response can be recorded on an EEG and they can spell the word. Although a simple technology compared to the momentous promises that other BCI companies make, the P300 system has granted otherwise debilitated patients a fraction more independence than they otherwise would have had.

From the first trepanation to the marriage of mind and machine, we have come a long way. However, there are many more questions to be answered. Brain computer interfaces have materialised metaphors; by establishing intricate links between our brains and computers, can we enter a 'matrix', or become 'brains in a vat'? Will we overcome current limitations in BCIs and have chips in our brains? Will we have answers, or simply more questions? Our attempts, and successes at touching the brain have prompted more ambitious work, but there is one important question to be answered: what happens when the dog catches its tail?

Fig.4: P3000 spelling system



Further Reading

Bartholow, R. (1874) 'Experimental investigations into the functions of the human brain', The American Journal of the Medical Sciences, (134), p. 305.

Cereletti, U. (1950) 'Old and new information about electroshock.', The American journal of psychiatry, 107(2), pp. 87–94. doi: 10.1176/ajp.107.2.87.

Faria, M. (2015) 'Neolithic trepanation decoded- A unifying hypothesis: Has the mystery as to why primitive surgeons performed cranial surgery been solved?', Surgical Neurology International. Medknow Publications. doi: 10.4103/2152-7806.156634.

Finger, S. (2010) Minds Behind the Brain: A history of the pioneers and their discoveries, Minds Behind the Brain: A history of the pioneers and their discoveries. Oxford University Press. doi: 10.1093/acprof:oso/9780195181821.001.0001.

Gardner, J. (2013) 'A history of deep brain stimulation: Technological innovation and the role of clinical assessment tools', Social Studies of Science, 43(5), pp. 707–728. doi: 10.1177/0306312713483678.

Gross, C. G. (2019) 'A Hole in the Head: A History of Trepanation', The MIT Press.

Harris, L. J. and Almerigi, J. B. (2009) 'Probing the human brain with stimulating electrodes: The story of Roberts Bartholow's (1874) experiment on Mary Rafferty', Brain and Cognition, 70(1), pp. 92–115. doi: 10.1016/j.bandc.2009.01.008.

Kennedy, P. R. and Bakay, R. A. E. (1998) 'Restoration of neural output from a paralyzed patient by a direct brain connection', NeuroReport, 9(8), pp. 1707–1711. doi: 10.1097/00001756-199806010-00007.

Kübler, A. (2020) 'The history of BCI: From a vision for the future to real support for personhood in people with locked-in syndrome', Neuroethics, 13(2), pp. 163–180. doi: 10.1007/s12152-019-09409-4.

Lozano, A. M. et al. (2019) 'Deep brain stimulation: current challenges and future directions', Nature Reviews Neurology. Nature Publishing Group, pp. 148–160. doi: 10.1038/s41582-018-0128-2.

Nijboer, F. et al. (2008) 'A P300-based brain-computer interface for people with amyotrophic lateral sclerosis', Clinical Neurophysiology, 119(8), pp. 1909–1916. doi: 10.1016/j.clinph.2008.03.034.

Suleman, R. (2020) 'A Brief History of Electroconvulsive Therapy', American Journal of Psychiatry Residents' Journal, 16(1), pp. 6–6. doi: 10.1176/appi.ajp-rj.2020.160103.

Wright, B. A. (1990) 'An Historical Review of Electroconvulsive Therapy', Jefferson Journal of Psychiatry, 8(10). doi: 10.29046/JJP.008.2.007.

King's College London Neuroscience Society National Conference 2021

"Touching the Brain"

Saturday 13th—Sunday 14th February 2021

Conference Programme

Saturday 13th February 2021

10:00-11:00	**Professor Alexander Hammers**, King's College London, UK Depth–EEG: a summary
11:00-12:00	**Professor Antonio Valentin**, King's College London, UK Deep Brain Stimulation for epilepsy
12:00-12:15	**Intermission**
12:15-13:15	**Professor Lorenzo Magrassi**, University of Pavia, Italy Deep Brain Stimulation in vegetative or minimally conscious patients
13:15-14:15	**Dr Aurore Thibaut**, University of Liege, Belgium Non-invasive brain stimulation for severely brain injured patients
14:15-14:30	**Intermission**
14:30-15:30	**Dr Ivana Rosenzweig**, King's College London, UK Non-invasive neurostimulation in the study of major sleep disorders
15:45-16:45	**Poster Presentations**, King's College London, UK Student Poster Presentations

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Sunday 14th February 2021

10:00-11:00	**Dr Mahnaz Arvaneh**, University of Sheffield, UK Brain-Computer Interfaces: algorithms, systems, adaptation, and applications
11:00-12:00	**Dr Sarah Chan**, University of Edinburgh, UK The ethical issues with Brain-Computer Interfaces and human enhancement
12:00-12:15	**Intermission**
12:15-13:15	**Dr Yoko Nagai**, Brighton & Sussex Medical School, UK Biobehavioural intervention for treatment of epilepsy
13:15-14:15	**Dr Su Metcalfe**, University of Cambridge, UK Nanomedicine for Central Nervous System diseases
14:15-14:30	**Intermission**
14:30-15:30	**Mr Mihail Dimitrov**, King's College London, UK Getting into a PhD in Neuroscience
15:45-16:45	**Mr Ryan Stanyard & Dr Matthew Kempton**, King's College London, UK British Neuroscience Association Presentation

Prof Alexander Hammers

King's College London, UK

Professor Alexander Hammers is Professor of Imaging and Neuroscience and Head of the King's College London & Guy's and St Thomas' PET Centre at St Thomas' Hospital.

His research area is medical imaging, in particular functional neuroimaging with quantified PET to understand mechanisms of neurological disease. Another area is structural neuroimaging using MRI and anatomical segmentation using a large manually annotated brain atlas database which his group has created over the past two decades. The main areas of application of his research are the epilepsies and neurodegenerative diseases, as well as methodological developments.

He will be presenting at the conference an overview of depth-EEG, an invasive form of bran monitoring, in the context of epilepsy surgery workup and research.

Prof Antonio Valentin

King's College London, UK

Dr Antonio Valentin is a clinical lecturer at KCL, whose research is mainly based in neuromodulation in patients with epilepsy. He and his team are working on new diagnostic and potential treatments for epilepsy, including different techniques using electrical and transcranial magnetic brain stimulation.

Dr Valentin is also an organiser of the lab research project module for the KCL Neuroscience course, as well as co-director of the International League Against Epilepsy (ILAE) VIREPA EEG Advanced course, intended for neurologists, neuropsychiatrists, neuropsychologists and epilepsy nurses. At the conference he will be elucidating the role of brain stimulation in patients with epilepsy.

Prof Lorenzo Magrassi

University of Pavia, Italy

Prof. Lorenzo Magrassi graduated in Medicine and Surgery at the Università degli Studi di Pavia, Italy, where he also specialised in Neurosurgery. Today he is associate professor of Neurosurgery and Director of the Scuola di Specialità in Neurochirurgia (Neurosurgical training program) at the Università degli Studi di Pavia. He is also research associate at the Istituto di Genetica Molecolare (Molecular Genetics Institute) of the CNR (National Research Council) in Pavia, and member of the NETS-IUSS Centre for Neurocognition and Theoretical Syntax.

His principal interests in the area of Clinical Neurosurgery are surgery of cerebral tumours (gliomas, meningiomas and schwannomas), and functional neurosurgery. He is the neurosurgeon behind the Cortical Activation by Thalamic Stimulation (C.A.T.S.) study (ClinicalTrials.gov Identifier: NCT01027572), one of the few recent studies on the efficacy of deep brain stimulation in vegetative or minimally conscious patients.

Dr Aurore Thibaut

University of Liege, Belgium

Dr Aurore Thibaut's research aims to improve the management of patients with brain injury through he application of novel non-invasive brain stimulation approaches. Dr Aurore Thibaut is co-director of the Coma Science Group. As a physical therapist, her work focuses on neurorehabilitation for patients with disorders of consciousness. Dr Thibaut's research mainly focuses on non-invasive brain stimulation in patients who had suffered from a severe brain injury with the aim to improve brain plasticity and facilitate their recovery. She published more than 90 papers and is leading several multicentre clinical trials. She is also working with neuroimaging and electrophysiology to objectify brain plasticity linked to these novel therapeutic approaches.

Dr Ivana Rosenzweig

King's College London, UK

Dr Ivana Rosenzweig heads the Sleep and Brain Plasticity Centre at the Institute of Psychiatry, Psychology and Neuroscience, King's College London (KCL), and she is Clinical Senior Lecturer in the Neuroscience of Sleep at KCL.

She obtained her MD from the University of Zagreb, Croatia, and her PhD from Trinity College, University of Cambridge, UK. She is an experienced consultant neuropsychiatrist with subspecialty expertise in sleep and neurophysiology, having trained and worked in university teaching hospitals in Cambridge and London. She is a recipient and a co-ordinator of the multidisciplinary and multi-site project in sleep research funded by the Wellcome Trust.

With her colleagues at the Centre for Neuroimaging Sciences at King's College London (KCL) and the Sleep Disorders Centre at Guy's Hospital, she founded the Sleep and Brain Plasticity Centre (SleepCity) at KCL. She is currently exploring the role of sleep on brain plasticity and cognition, both in clinical and preclinical studies, with a particular focus on the sleep oscillations.

Dr Mahnaz Arvaneh

University of Sheffield, UK

Dr Mahnaz Arvaneh has a Ph.D. in Advanced Brain-Computer Interfaces from Nanyang Technological University (NTU), Singapore. She has been attached researcher at the Institute for Infocomm Research (Agency for Science, Technology and Research, Singapore), lecturer in Biomedical Engineering at University College Dublin, Ireland, and research fellow at the Trinity College Institute of Neuroscience, Dublin, Ireland. Since September 2015, she has been a lecturer in the Department of Automatic Control and Systems Engineering at the University of Sheffield, UK.

Dr Arvaneh is an expert in Brain-Computer Interfaces and neural signal processing, and in their applications in physical and mental health. She is the director of the Physiological Signals and Systems Laboratory at the University of Sheffield. Her work on neural interfaces has received high-profile media coverage, and she has published more than 50 highly cited papers in both engineering and neuroscience top-ranked journals and conferences. Since March 2018, she has been serving as associate editor of IEEE Transactions on Neural Systems and Rehabilitation Engineering. She also co-edited a book on Brain-Computer Interfaces in the IET (Institution of Engineering and Technology) and contributed to the Royal Society Neural Interfaces Perspective, launched in September 2019.

Dr Sarah Chan

University of Edinburgh, UK

Dr Sarah Chan has a wide interest in the ethics of medical research including stem cells, embryo research and reproductive medicine. Human enhancement, gene therapy and genetic modification, along with animal ethics and research ethics, are also some of her areas of study. Dr Chan completed her undergraduate degrees in law and biological sciences at the University of Melbourne, Australia, and she earned a PhD in healthcare ethics from the University of Manchester. She was appointed Research Fellow in Bioethics and Law at the University of Manchester in 2005, and Deputy Director of the Institute for Science, Ethics and Innovation in 2009. After moving to the University of Edinburgh, in 2016 she was awarded a Wellcome Trust seed grant to investigate the relationships between social media and health. Dr Chan is also popular science communicator: she has delivered lectures at institutions such as the Max Planck Institute of Neurobiology, the Royal Society and the Nuffield Council on Bioethics. She was elected to the Royal Society of Edinburgh in 2018, and she serves on the Genomics England Ethics Advisory Committee and on the Scottish Genomes Partnership. She contributed to the Royal Society Neural Interfaces Perspective, launched in September 2019.

Dr Yoko Nagai

Brighton & Sussex Medical School, UK

Dr Yoko Nagai: Dr Yoko Nagai is a translational neuroscientist with interests in mind-body interaction and human consciousness. Her main work involves the investigation and development of a non-drug therapy for patients with drug-resistant epilepsy. The therapy is termed as Autonomic Cognitive Rehabituation training (ACRT). This pioneering work attracted funding for clinical trials from various grant bodies (Bial Foundation, Tourette Syndrome Association USA, Wellcome Trust). More recently, her research interests expanded from human wellbeing to social wellbeing, integrating her educations in science, business and law. She is a member of International League Against Epilepsy (ILAE: UK), American Epilepsy Society and Inns of Court. She was awarded Gowers Clinical Science Award, International League Against Epilepsy (ILAE) UK in 2016.

Dr Su Metcalfe

University of Cambridge, UK

Dr Su Metcalfe: Is a senior research associate at Cambridge working on the application of nanotechnology to healthcare - nano-medicine - now recognised worldwide as a new era in clinical medicine. By loading biocompatible, biodegradable nano-particles with growth factor, and targeting to sites of tissue damage, a synthetic biologically instructive niche can be created to repair tissues in situ, and/or to support cell survival in regenerative cell therapy. MULTIPLE SCLEROSIS: The nano-therapeutic approach is being used to target 'LIF' to treat MS. LIF is a stem cell growth factor involved in myelin repair and neuroprotection, in addition to being tolerogenic for myelin. These three core properties of LIF provide a potentially curative therapy for early stage MS, whilst providing a valuable adjunct to current DMT used to treat MS. 2013: founded LIF-NanoRx Ltd to deliver LIFNano to patients - see LIFNano.com..

AWARDS: 2014 Global GMSI Prize. 2017 Business Woman of the Year, Judge Business School. 2017 Global Award for NanoMedicine.

Mr Mihail Dimitrov

King's College London, UK

Mihail Dimitrov: PhD Researcher at the Institute of Psychiatry, Psychology & Neuroscience on Pharmacological neuroimaging of Autism. His academic journey took him all the way from studying cell models (during BSc) through working with post-mortem rodent brains all the way up to studying human brains in vivo.

Interests include:

- Neurodevelopmental and psychiatric disorders
- AI-fuelled computational modelling of brain phenomena
- Multi-modal neuroimaging (incl. MRI, EEG and PET)
- Pharmacological probing
- Multi-disciplinary and translational research

Mr Ryan Stanyard

King's College London, UK

Early Career Cognitive Neuroscientist, with experience in research in neuroscience streams (IoPPN, King's College London; CDR, Universiti Sains Malaysia; School of Life Sciences, Keele University) and neuropsychological streams (IoPPN, KCL; School of Psychology, Keele University). A keen advocate of STEM education and scientific outreach, I engage with a number of mentoring and outreach initiatives.

Part of King's College London's MRC Biomedical Imaging Groups, I focus on investigating the relationship between the structural and functional brain connectomes over the lifespan. Specifically, my interest lies in how the coupling of these connectomes differs between individuals within the autistic spectrum and those who are neurodevelopmentally typical. The approach of my team leverages whole brain computational models alongside empirical data from diffusion imaging, functional and structural MRI and clinical covariates to explore how nodal changes in excitation inhibition, state transitions and connectivity coupling occur across time and nodal space.

Dr Matthew Kempton

King's College London, UK

My main interests are neuroimaging (particularly structural MRI) in psychosis disorders such as schizophrenia and bipolar disorder. I coordinate the EU-GEI High Risk Study with Prof Philip McGuire and Dr Lucia Valmaggia and I lead a longitudinal multicentre neuroimaging in this cohort of individuals at risk of psychosis. In addition to characterising changes in brain structure in psychiatric disorders, our group are working to increase the sensitivity of structural MRI to <1% changes in brain volume. To clarify changes in brain structure I have worked on a number of meta-analyses looking at Schizophrenia, Bipolar Disorder, Major Depression and PTSD. I'm grateful to be currently funded by the NIHR Maudsley Biomedical Research Centre to predict individualised outcome in patients at risk of psychosis, and have previously been funded by the MRC, Wellcome Trust and EU.

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