What has been the biggest development in the clinical neurosciences over the last 10 years?

Clinical neuroscience is the study of diseases of the nervous system and their treatments. The term can be applied broadly, for example the Journal of Innovation in Clinical Neuroscience includes neurological, psychiatric and neurosurgical disorders[i]. It is informed by both clinical practice and neuroscience. This grounding in clinical practice means developments can be quantified by their effects on numbers of individual patients: a bigger development will create greater value for a greater number of patients. Big developments in the neuroscience of diseases are not sufficient to be big developments in clinical neurosciences. For example, identifying the β-amyloid pathology in Alzheimer's has been scientifically revolutionary but has not yet created significant therapeutic value for large numbers of patients[ii]. Therefore, the most significant development in clinical neuroscience needs to be both specific to patients with nervous system disease and help a large number of those patients.

The last decade has been revolutionary in neuroscience,[iii,iv] with steadily increasing numbers of articles published (Figure 1). One overarching theme has been the definition and isolation of neural circuits: arrays of neurons that correspond to sensory, motor or cognitive functions. The 2014 Nobel Prize in Physiology or Medicine was awarded for "discoveries of cells that constitute a positioning system in the brain"[v]. Advances in molecular genetics, such as Nature's 2010 ''Method of the Year'' optogenetics, has allowed researchers to manipulate specific components of these circuits[vi]. One of the largest neuroscience initiatives in history, the 1.2-billion-euro Human Brain Project (2013) has promised that supercomputer-scale models of these circuits will elucidate neurological disorders such as Alzheimer's[vii,viii]. The 2014 World Cup kicked off with a paraplegic man using a brain-machine interface and robot exoskeleton; further circuit modelling is proposed as key to optimising these devices[ix]. Even schizophrenia, OCD, anxiety disorders, depressive disorders and substance use disorders have been re-conceptualised as disorders of neural circuits with the promise that the conceptual and technological revolutions will eventually provide value to these large groups of patients[x]. Neuroscience in the 2010s has been revolutionary, but as observed in Roy Porter's History of Medicine, knowledge has changed much faster than therapies[xi,xii].

The translation of scientific discovery into medical therapy also depends on contextual factors. Medical innovations are hampered by the costs of development and mass production, safety concerns and catering to more complex disease aetiologies. Furthermore, even the cheapest and easiest to implement medical innovations can be rejected if they are not presented at the right time. For instance, handwashing with disinfectant was rejected when proposed in 1846 by Ignaz Semmelweis because he lacked the context of Germ Theory to explain his scientific findings[xiii]. New scientific understanding does not immediately shift medical practice, it can require decades of work before significant value is created for patients. This likely also applies to the recent conceptual revolutions in neuroscience. Therefore, we need to identify a medical development that applies specifically to patients with neurological diseases, has existed in the right time and context to be implemented, and has created value for a large number of patients.

The WHO figures for burden of neurological disease (2016) use disability-adjusted life years (DALYs), including both years lost to death and to disability (Figure 2)[xiv]. Globally, stroke accounts for a significant majority of the neurological DALYs, 2.5 times as many as the next highest disease, migraine. Understandably, a disease with such a high prevalence is treated by many medical professionals outside of clinical neurosciences, especially if preventative medicine is included. However, much of the burden of stroke care in Europe falls to clinical neuroscience teams in acute care, and during physical and psychological rehabilitation. Stroke symptoms are due to neural tissue damage, meaning it is addressed by clinical

neuroscience, even though its cause is vascular. Stroke research by neuroscientists has strongly emphasised the importance of early reperfusion to prevent irreversible tissue damage[xv]. The necessity for early reperfusion has synergised with innovations in medical treatment, spurring the development of reperfusion technologies: thrombolytics and mechanical thrombectomy. This essay will focus on mechanical thrombectomy since a significant proportion of the development, and implementation, of thrombolytics predated the last decade. Mechanical thrombectomy draws on both neuroscience and medical practice and has been successfully implemented in the last 10 years, creating value for the patient group with the largest burden of neurological disease.

Mechanical thrombectomy uses a catheter threaded through an artery into the area of occlusion. A stent is then deployed, a mesh unfolds, seizes and removes the clot[xvi]. Initial success came with the first generation of helical snare retrievers, the MERCI devices, FDA approved in 2004[xvii]. These achieved revascularisation, measured as Thrombolysis In Myocardial Infarction (TIMI), grade ≥2 in all treatable vessels in 48% of patients[xvii]. The second generation, Penumbra Thromboaspiration System built on this by using a microwire repeatedly passed through the clot to break it up while under aspiration. It received FDA approved in 2007. This achieved better revascularisation rates of 81.6% TIMI≥2, but poorer clinical outcomes at 30-day follow-up with a mortality rate of 33%[xvii].

The stentrievers, Solitaire FR and Trevo Pro, both FDA approved in 2012, combined elements of the previous tools. These introduce a stent that pushes a thrombus onto the artery wall to first achieve reperfusion. After 3-5 minutes the microcatheter and stentriever are removed together under aspiration. The TREVO 2 trial of Trevo Pro showed a thrombolysis in cerebral infarction (TICI)[1] score ≥2 of 86% compared to MERCI devices at 60%. Further, there was no significant difference in safety, including intracerebral haemorrhage, procedure-related complications and mortality.

The most significant clinical trial in the last decade was MR CLEAN (2015)[xviii,xix]. Stentrievers were used in 190 of the 233 patients (81.5%) assigned to the intraarterial treatment group within six hours of symptom onset. A meta-analysis of this and four other trials, performed by the HERMES collaboration, found that, in patients with large-vessel occlusion in anterior circulation treated within six hours, 5.1 patients needed to be treated with mechanical thrombectomy for one patient to have improved functional outcome at 90 days. Furthermore, there was no significant difference in mortality or intracranial haemorrhage incidence. These results were corroborated by the UK PISTE trial (2016)[xx], which showed that patients who had both thrombolysis and mechanical thrombectomy were 20% more likely to have made a full neurological recovery compared to thrombolysis alone.

Mechanical thrombectomy is continuing to be improved. In 2018, the American Stroke Association recommended an increased treatment window for clot removal from 3 hours to 4.5 hours[xxi]. This was based on the DAWN (2018) and DEFUSE 3 (2018) trials. Thrombectomy, even outside the optimum treatment window, showed on average only 3.5 patients needed to be treated for one patient to have significantly improved functional outcomes at 90 days.

Not only has mechanical thrombectomy been shown to be effective, been successfully implemented and helped a large number of neurological patients, it also has the capacity to go further. The NHS Long Term Plan[xxii] aims for 8000 mechanical thrombectomies per year in England by 2022, over the 1100 in 2018-2019[xxiii]. The disease burden of stroke disproportionately comes from the 30-50% of patients with proximal large artery occlusion. Increasing access to thrombectomy will therefore significantly reduce DALYs for many patients[xxiv]. Further innovations in acute stroke care include ways of getting patients

[1] TIMI and TICI scores both describe revascularisation rates in these studies

treatment as soon as possible[xxv,xxvi]. This can synergise with wider technological shifts. For example, the COVID-19 pandemic has increased the use of telemedicine networks, allowing doctors to remotely review scans and recommend appropriate patients for thrombectomy[xxvii].

Mechanical thrombectomy in stroke teaches us that innovations that are essential to the betterment of clinical neurosciences are not necessarily bottom-up from basic neuroscience research, but are heavily influenced by other medical fields. Basic research may further develop this therapy by elucidating the pathophysiology and its mitigants, potentially increasing the time window for intervention. However, it is also important to view success stories in the history of medicine as partially dependent on basic science, clinical research, interdisciplinary medicine, increasingly greater collaborative efforts and the serendipity needed to bring these elements together at the right moment in time.

Figure 1

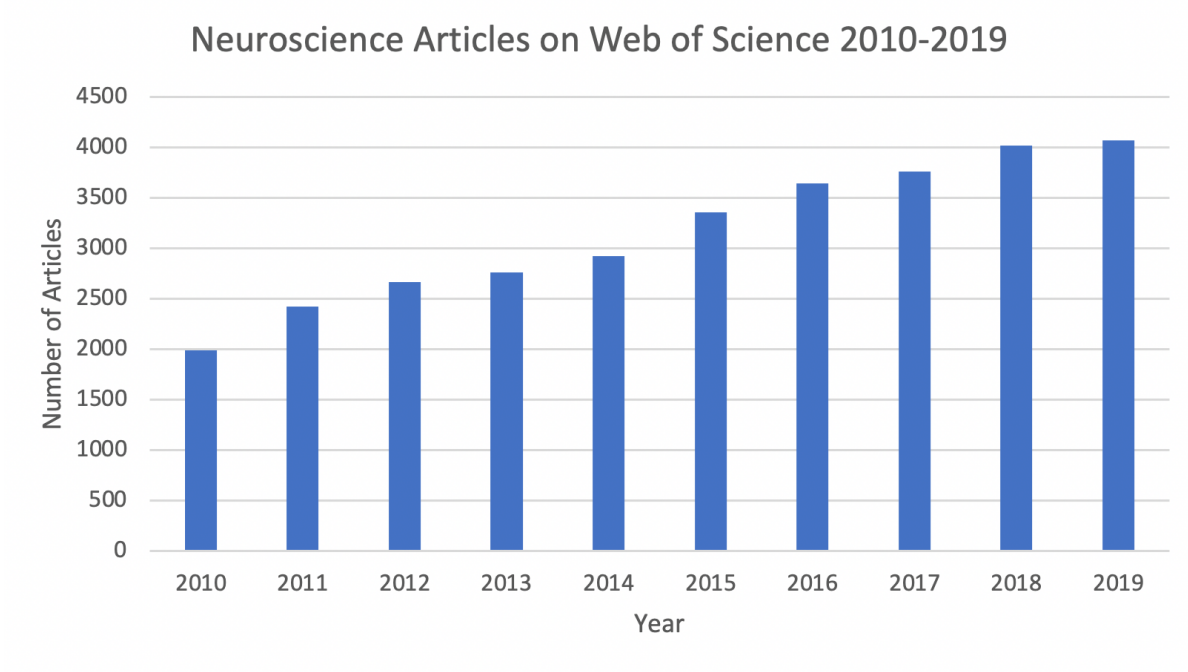

Figure 2

WHO Burden of Neurological Disease Global Numbers ($\times 10^3$) (2016)

Disorder	Absolute Deaths	Percentage Deaths	Absolute DALYs	Percentage DALYs
All neurological disorders	9039	100%	276143	100%
Stroke	5528	61%	116445	42%
Migraine	0	0%	45122	16%
Alzheimer's	2382	26%	28764	10%
Meningitis	318	4%	21866	8%
Idiopathic epilepsy	126	1%	13492	5%
Spinal Cord Injuries	0	0%	9522	3%
Traumatic Brain Injury	0	0%	8000	3%
Brain and other CNS cancer	227	3%	7660	3%
Tension-type headache	0	0%	7195	3%
Encephalitis	103	1%	6704	2%
Other neurological disorders	53	1%	3695	1%
Parkinson's	211	2%	3235	1%
Tetanus	37	0%	2367	1%
Multiple sclerosis	19	0%	1151	0%
Motor neuron disease	34	0%	926	0%

References

[i] Innovations in Clinical Neuroscience. (n.d.). Innovations in Clinical Neuroscience. [online] Available at: https://innovationscns.com/ [Accessed 28 Aug. 2020].

[ii] Gold M. Phase II clinical trials of anti-amyloid β antibodies: When is enough, enough?. Alzheimers Dement (N Y). 2017;3(3):402-409. Published 2017 May 17. doi:10.1016/j.trci.2017.04.005

[iii] Celebrating a decade of progress. Nat Neurosci 2, 487 (1999). https://doi.org/10.1038/9131

[iv] Neuroscience Cara M. Altimus, Bianca Jones Marlin, Naomi Ekavi Charalambakis, Alexandra Colón-Rodríguez, Elizabeth J. Glover, Patricia Izbicki, Anthony Johnson, Mychael V. Lourenco, Ryan A. Makinson, Joseph McQuail, Ignacio Obeso, Nancy Padilla-Coreano, Michael F. Wells The Next 50 Years of, for Training Advisory Committee Journal of Neuroscience 2 January 2020, 40 (1) 101-106; DOI: 10.1523/JNEUROSCI.0744-19.2019

[v] All Nobel Prizes in Physiology or Medicine. (2019). NobelPrize.Org. https://www.nobelprize.org/prizes/lists/all-nobel-laureates-in-physiology-or-medicine/

[vi] Method of the Year 2010. Nat Methods 8, 1 (2011). https://doi.org/10.1038/nmeth.f.321

[vii] Amunts, K., Ebell, C., Muller, J., Telefont, M., Knoll, A., & Lippert, T. (2016). The Human Brain Project: Creating a European Research Infrastructure to Decode the Human Brain. Neuron, 92(3), 574–581. https://doi.org/10.1016/j.neuron.2016.10.046

[viii] Theil, S. (n.d.). Why the Human Brain Project Went Wrong—and How to Fix It. Scientific American. Retrieved August 28, 2020, from https://www.scientificamerican.com/article/why-the-human-brain-project-went-wrong-and-how-to-fix-it/

[ix] BBC News. 2020. Paraplegic Kicks Off World Cup. [online] Available at: <https://www.bbc.com/news/science-environment-27812218> [Accessed 26 August 2020].

[x] McTeague LM, Rosenberg BM, Lopez JW, Carreon DM, Huemer J, Jiang Y, et al. Identification of Common Neural Circuit Disruptions in Emotional Processing Across Psychiatric Disorders. Am J Psychiatry (2020) 177(5):411–21. doi: 10.1176/appi.ajp.2019.18111271

[xi] Rego MD. Counterpoint: clinical neuroscience is not ready for clinical use. Br J Psychiatry. 2016;208(4):312-313. doi:10.1192/bjp.bp.115.170878

[xii] Porter, R. (2001). The Cambridge illustrated history of medicine. Cambridge ; New York: Cambridge University Press.

[xiii] D. Gillies Hempelian and Kuhnian approaches in the philosophy of medicine: the Semmelweis case Studies in History and Philosophy of Science Part C: Studies in History and Philosophy of Biological and Biomedical Sciences, 36 (1) (2005), pp. 159-181

[xiv] WHO | Metrics: Disability-Adjusted Life Year (DALY). 2020. WHO | Metrics: Disability-Adjusted Life Year (DALY). [ONLINE] Available at: https://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/. [Accessed 26 August 2020].

[xv] Xing, C., Arai, K., Lo, E. H., & Hommel, M. (2012). Pathophysiologic cascades in ischemic stroke. International journal of stroke : official journal of the International Stroke Society, 7(5), 378–385. https://doi.org/10.1111/j.1747-4949.2012.00839.x

[xvi] Bruce C.V. Campbell, MBBS, PhD, FRACP, Atte Meretoja, MD, PhD, Geoffrey A. Donnan, MD, FRACP, and Stephen M. Davis, MD, FRACP Twenty-Year History of the Evolution of Stroke Thrombolysis With Intravenous Alteplase to Reduce Long-Term Disability

[xvii] Boyle, K., Joundi, R.A. & Aviv, R.I. An historical and contemporary review of endovascular therapy for acute ischemic stroke. Neurovasc Imaging 3, 1 (2017). https://doi.org/10.1186/s40809-016-0025-2

[xviii] O'Carroll CB, Rubin MN, Chong BW. What is the Role for Intra-Arterial Therapy in Acute Stroke Intervention?. Neurohospitalist. 2015;5(3):122-132. doi:10.1177/1941874415587681

[xix] Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. N Engl J Med. 2015;372(1):11–20. https://doi.org/10.1056/NEJMoa1411587.

[xx] Stroke Association. 2020. PISTE trial provides new evidence for effectiveness of thrombectomy treatment in the UK | Stroke Association. [ONLINE] Available at: https://www.stroke.org.uk/news/piste-trial-provides-new-evidence-effectiveness-thrombectomy-treatment-uk. [Accessed 26 August 2020].

[xxi] Robinson T, Zaheer Z, Mistri AK. Thrombolysis in acute ischaemic stroke: an update. Ther Adv Chronic Dis. 2011;2(2):119-131. doi:10.1177/2040622310394032

[xxii] NHS. The NHS Long Term Plan. London: NHS, 2019. Available at: www.longtermplan.nhs.uk/publication/nhs-long-term-plan/

[xxiii] Ford G, James M, White P. Mechanical thrombectomy for acute ischaemic stroke: an implementation guide for the UK. Oxford: Oxford AHSN, 2019. Available at: www.oxfordahsn.org/our-work/adoptinginnovation/mt-guide/

[xxiv] NHS England 170033P, 2018 Available at: https://www.england.nhs.uk/midlands/wp-content/uploads/sites/46/2019/05/d04-mechanical-thrombectomy-for-acute-ischaemic-stroke-v2.pdf

[xxv] HQSCNZ (2018). Century of the System, Dr Atul Gawande. YouTube. Available at: https://www.youtube.com/watch?v=o5NP0KKQLJU [Accessed 27 Aug. 2020].

[xxvi] Philips. 2020. How we can build a brighter future for stroke patients - Blog | Philips. [ONLINE] Available at: https://www.philips.com/a-w/about/news/archive/blogs/innovation-matters/20191129-how-we-can-build-a-brighter-future-for-stroke-patients.html. [Accessed 26 August 2020].

[xxvii] French B, Day E, Watkins C, McLoughlin A, Fitzgerald J, Leathley M, Davies P, Emsley H, Ford G, Jenkinson D, et al. The challenges of implementing a telestroke network: a systematic review and case study. BMC Med Inf Dec Making. 2013;13(1):125