

# INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACEUTICAL SCIENCES

Published by JK Welfare & Pharmascope Foundation Journal Home Page: https://ijrps.com

## **Cortical Implants in Cerebrum - A Review**

Rieshy V<sup>1</sup>, Yuvaraj Babu K $^{*1}$ , Gayatri Devi R $^{2}$ 

<sup>1</sup>Department of Anatomy, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India <sup>2</sup>Department of Physiology, Saveetha Dental College and Hospitals, Saveetha Institute of Medical and Technical Sciences (SIMATS), Saveetha University, Chennai, Tamil Nadu, India



## \*Corresponding Author Name: Yuvaraj Babu K Phone: +91-9840210597

Email: yuvarajbabu@saveetha.com

ISSN: 0975-7538

DOI: https://doi.org/10.26452/ijrps.v11iSPL3.3355

Production and Hosted by

IJRPS | https://ijrps.com

© 2020 *|* [All rights reserved.](https://doi.org/10.26452/ijrps.v11iSPL3.3355)

## **INTRO[DUCTION](https://ijrps.com)**

The cortical implant is neuroprosthetic which is a direct bridging link to the cerebral cortex of the

brain. It provides stimulation and has different benefits depending upon the type of design and the placement of the implant. It is a typical cortical with a microelectrode array, a small device that transmits or receives the neural signal. Its main goal is to replace the neural circuitry in the brain that no longer functions properly. It has a wide variety of potential uses from restoring vision to helping patients who suffer from dementia. Vision is restored when the visual cortex is directly stimulated. Recent studies show that there has been a development in developing an effective auditory prosthesis that directly interfaces the auditory cortex. Whereas, some implants are designed to improve the cognitive function. These implants are placed on the prefrontal cortex. Prefrontal Cortex is helpful in restoring the attention that helps in decision making. The cerebrum is the largest part of the brain. The cortical implant is responsible for the integration of complex sensory and neural functions which helps in the initiation and coordination of voluntary activity. Brain implants technology and records voltage signals during cognitive tasks (deCharms *et al.*, 1999). These implants have the biggest advantages of being directly interfaced with the cortex. These implants act as a replacement that replaces the damaged tissues in the cortex. Bi[omimicry is an alterna](#page-4-0)te pathway for signals.

There is some previous research. It is important to record the histopathological evaluations of the materials that are used to implant in the cerebral cortex (Stensaas and Stensaas, 1978). Usage of silicon as a substrate in the microelectrode arrays in the cerebral cortex for chronic neural reading and the histological analysis of tissue (Vetter, 2004). Charact[eristics of microelectrode ar](#page-5-0)rays that have been implanted in the cerebral cortex for long term recording (Williams *et al.*, 1999). The biocompatibility of neural implants and inserta[ble mi](#page-6-0)c[roelec](#page-6-0)trode arrays were studied (Edell *et al.*, 1992). The tissues were more reactive when silicon was used as a biocomp[atible material, but rel](#page-6-1)atively severe reactions had been anticipated. The neural interface of cortical vision prosthesis is [a place where the](#page-4-1) stimulation of a large number of cortical neurons takes place (Normann, 1999). It provides proof of concept for the cortically based artificial vision. There have been recent advances in the materials and system devices that are used for the neural interface (Won, 2018)[. It provides a](#page-5-1) long-lived optical or electrical interface to the neural systems that play a critical role in the neuroscience research in the development of non-pharmacological treatments in c[ase of](#page-6-2) [neuro](#page-6-2)logical disorders. These advances were established as a foundation of architecture in the optical or electrical neural interface for the future that is blurring of the lines between the biotic and the abiotic systems for the progression in neuroscience research for the welfare of the human being.

Over the past years various research done by our team was on osteology (Choudhari and Thenmozhi, 2016), foramina in middle cranial fossa (Hafeez and Thenmozhi, 2016), styloid process (Kannan and Thenmozhi, 2016), foramen of Huschke (Keerthana and Th[enmozhi,](#page-4-2) 2016), [foramen me](#page-4-2)n[ingo-o](#page-4-2)rbitale (Pratha and Thenmozhi, 2016), [girdy's tubercle \(Nandhini](#page-4-3) *et al.*, 2018), Occipi[tal emissary formanen \(Subashri](#page-4-4) and Thenmozhi, 2016), [stature estimation \(Krishna and Babu](#page-4-5), 2016), radiation effects of [mobile phone \(Sriram](#page-5-2) *[et al.](#page-5-2)*, 2015), use of i-pads [in education \(Th](#page-5-3)[e](#page-5-4)[jeswa](#page-5-3)[r](#page-5-4) and Thenmozhi, 2015), on micro RNA (Johnson, 2020), microRNA especially on preeclampsia patients (Sekar, 2019), animal studies (Seppan *et al.*, 2018), and in few other fields like thyroid [function \(Menon and Th](#page-5-7)enmozhi, 2016), a[nd ambly](#page-4-6)[opia](#page-4-6) (Samuel and Thenmozhi, 2015). There was not much [work done o](#page-5-8)n cortical implants[; hence](#page-5-9) [the aim of th](#page-5-9)e present review is to elaborate about the impo[rtance to replace the neural](#page-5-10) circuitry in the br[ain that no longer functions pro](#page-5-11)perly. It helps the patients who have neurological disorders and to those who have difficulty in complex sensory and neural functions. Cortical implants are the visual implants for optics. Auditory implants are for hearing. Cognitive implants are for attention and decision making—brain-computer interface. The biggest advantage of neuroprosthesis is that it is directly interfaced with the cortex. It is a replacement that is done to the damaged tissues in the cortex.

#### **Methodology**

This review was done based on the articles obtained from Various platforms like PubMed, PubMed Central and Google scholar. They were collected with a restriction on a time basis from 1970 - 2020. The inclusion was original research papers, in vitro studied among various conditions and articles that contain pros and cons. Exclusion criteria came into account for review articles, retracted articles and articles of other languages. All the articles were selected based on Cortical Implants in Cerebrum.

They are determined by article title, abstract and complete article. When article holder websites were analyzed on the topic of Cortical Implants in Cerebrum, more than 2000 articles and based articles were found, when it was shortlisted based on the inclusion and exclusion criteria, the number of articles was lowered to 130 articles. When the timeline and other factors were quoted, only 31 articles came into play. This article is reviewed from the 31 articles collected. Quality of articles used was assessed using a quality assessment tool and graded as strong, moderate and weak (Table 1).

#### **Implant materials**

Silicon is suitable for long term recording of the cerebral cortex and acts as an effe[ct](#page-2-0)ive platform technology for the foundation of the neural interface in humans (Vetter, 2004). Polymers are common material that acts as both substrate and insulation material for metals and interconnection of wires in the electrode sites (Hassler *et al.*, 2011). Advances in the [neurotechnol](#page-6-0)ogies that revolutionized scientific treatment help in the prevention of a variety of neurological disor[ders \(Wellman](#page-4-7), [2018\)](#page-4-7).

S.No	Author	Year	Type of study	Key points	Quality of study
$\mathbf{1}$	David T. Blake	1999	Research	Implant technol- ogy and records signals	Moderate
$\overline{2}$	Suzanne S Sten- saas	1978	Research	Histopathological evaluations	Moderate
3	R. J. Vetter	2004	Research	Chronic neural reading	Strong
4	Robert L. Ren- naker	1999	Research	Characteristics of micro elec- trode array	Moderate
5	D. J. Edell	1992	Case study	biocompatibility	Moderate
6	Richard A. Nor- mann	1999	Case study	Neural interface	Moderate
7	Sang Min Won	2018	Case study	Recent advances	Moderate
8	<b>Tim Boretius</b>	2010	Research	Polymers as common mate- rial	Moderate
9	James R. Eler	2018	Research	neurotechnologies Strong	
10	M. Gulino	2019	Case study	Field brain machine inter- face	Moderate
11	Justin C. Williams	2000	Case study	Working span	Strong
12	Taylor. D	2002	Research	Control of implants	Strong
13	Paninski. L	2002	Research	Control move- ment	Moderate
14	Andrew <b>B.</b> Schwartz	2004	Research	Extraction of algorithms	Moderate
15	Normann. R. A	1996	Research	Ultra intra cor- tical electrode array	Moderate
16	Fernandez. E	2000	Research	Relative move- ments	Strong
17	Gary Keib	2001	Case study	Cellular synaptic elements	Strong
18	Rousche PJ	2001	Research	Advanced neu- roprosthetic systems	Moderate
19	Rohde MM	2000	Research	Direct brain interface	Strong

<span id="page-2-0"></span>**Table 1: Quality of study for articles used in review**

Field brain-machine interface is growing as the most important source of progress in neuroscience research (Gulino, 2019). Needles made up of plastic araldite were implanted in the cerebral cortex that changes indwelling when inserted in a foreign body (Stensaas and Stensaas, 1976). Cobalt, a toxic material, [has extensive](#page-4-8) changes in the zones of connective tissue, astrocytes indicate that materials that are tolerated by the brain are used in the fabrication of neu[roprosthetic devices \(Stensa](#page-5-12)as and Stensaas, 1978).

## **Biocompatibility**

The model system has va[rious advances in the](#page-5-0) [bioco](#page-5-0)mpatibility of neural implants for the development of the cortical component in the neural implant's working span (Kipke, 2003).

### **Control of cortical implant prosthesis**

3D movement neuroprosthetic devices are controlled by the activity o[f cortical ne](#page-4-9)urons through the usage of algorithms that are used to decode the movement in real-time (Taylor *et al.*, 2002). Electrode array for human use is a neurally based control movement that is feasible for paralysed humans (Serruya *et al.*, 2002). Control of prosthesis through cortical signa[ls three elements i](#page-5-13)n the chronic microelectrode arrays for the extraction of algorithms in the prosthetic effectors (Schwartz, 2004).

## **Microelectrode arrays**

Ultra intracortical electrode array is a co[mbination](#page-5-14) [of a l](#page-5-14)arge number of electrodes that is suited for parallel processing mechanism in the cortex (Fernandez *et al.*, 2014)—minimizing the relative movements in the neural tissues to embrace the capacity of the microelectrode array (Maynard *et al.*, 2000). Multi-site unit recordings in the cerebral c[ortex](#page-4-10) [awake animals in th](#page-4-10)e period of time (Williams *et al.*, 1999).

Neuro cortex in the human br[ain has cellular](#page-5-15), [synap](#page-5-15)tic elements that are arranged in laye[rs \(Scherf](#page-6-1) *et al.*, [2006](#page-6-1)).

Advanced neuroprosthetics systems improve the quality of life of deaf, blind and paraly[sed popula](#page-5-16)[tions](#page-5-16) (Rousche *et al.*, 2001; Johnson, 2020).

## **Interface**

Cases considered for appropriate operation act as a dire[ct brain interface \(L](#page-5-17)[evine,](#page-4-6) 20[00\).](#page-4-6) Adequate recognition provides an effective engagement in the new communication of motor disabilities (Babiloni, 2010). Brain modulates cortical responses that are prescribed by operantc[onditioning r](#page-5-18)ules (Kipke, 2003).

### **Cochlear implant**

Central auditory pathways are limited in age groups and implantation occurs with benefits. These are a limited number of implantations in congenitally deaf children (Gilley *et al.*, 2008). Neurocognitive processing for the auditory input and the type of changes that are adequately processed in cochlear implants in children (Torppa *et al.*, 2012). Childhood deafness [seeks to restore th](#page-4-12)e normal development function and cerebral auditory function (Gordon, 2011). Post lingually deafened subjects having a hearing of speech t[hrough the cochlear](#page-5-19) implants that had increased activation in both the temporal and frontal cortices (Hirano, 2000). Prospectiv[e lon](#page-4-13)[gitudinal d](#page-4-13)esigns can track dynamics in the cortical plasticity before and after implantation (Stropahl *et al.*, 2017). Residual takeover persists after adaptation in cochlear i[mplants](#page-4-14), [need](#page-4-14) not be necessarily maladaptive (Stropahl *et al.*, 2015). Effects in place of stimulation, cortical auditory evok[ed poten](#page-5-20)[tials in the](#page-5-20) speech performance in the cochlear implant listeners (Mamelle *et al.*, 2017). After cochlear implant[ation, speech unders](#page-5-21)tanding has been improved and speech and noise were spatially separated (Legris, 2018).

#### **Research on rats**

Insulin-producing cells and mesenchymal stroma cells are pr[otective again](#page-5-22)st cognitive impairment in the implant site of diabetic rats (Wartchow, 2020). Stimulation threshold has an efficient design in retinal and visual and cortical implants in rats (Xie *et al.*, 2019). The response of visual cortical neurons in the mouse, intraocular a[nd extraocular ar](#page-6-3)e stimulated by electrical signals in the retina (Ryu and Fried, 2018). The results indicate a therap[eu](#page-6-4)[tic ac](#page-6-4)t[ivity](#page-6-4) towards the sustainment of the penile erection within the presence of an extract in aged rats (Seppan *et al.*, 2018).

## **[Future Researc](#page-5-23)h**

Diabetes mellitus is a public health problem and can caus[e long term damage](#page-5-9) in the brain that results in cognitive impairment (Wartchow, 2020).

## **RESULTS AND DISCUSSION**

Silicon material is use[d for long](#page-6-3) t[erm r](#page-6-3)ecording of the cerebral cortex. This technology lays a foundation for the neural interface in humans. Needles made up of plastic araldite that are implanted in cerebral cortex indwells when inserted in a foreign body. Cobalt which is a toxic metal that leads to extensive changes in the connective tissue and astrocytes indicates the materials that are tolerated by the brain and help in the fabrication of neuropros-

thetics devices (Stensaas and Stensaas, 1978; Kipke, 2003).

Childhood deafness seeks restoration in the normal development function of cerebral auditory function. Prospecti[ve differs from longitudinal](#page-5-0) [design](#page-4-9) [and c](#page-4-9)ould track dynamics and cortical plasticity before and after implantation. Residual takeover persists after adaptations and cochlear implants are need not be necessarily maladaptive (Maynard *et al.*, 2000; Gordon, 2011; Stropahl *et al.*, 2015).

The limitation of the review is this study is the intramural cortical microstimulation that evokes a behavioural respon[se, penetrating](#page-5-21) [into the Utah](#page-5-15) [intrac](#page-5-15)[ortical e](#page-4-13)l[ectrod](#page-4-13)e array.

The future scope of the cortical implant is that the insulin-producing cells and mesenchymal stroma cells are protective against cognitive impairment in the implant site of diabetic rats.

## **CONCLUSION**

From this review, it can be concluded that cortical implants are placed to replace the neural circuitry in the brain that no longer functions properly. It helps patients with neurological disorders. It helps patients who have difficulty in complex sensory and neural functions. Visual implants are for optics. Auditory implants are for hearing. Cognitive implants are for attention and decision making. The biggest advantage of neuroprosthetics is that it is directly interfaced with the cortex. Lots of improvements are expected to happen in the near future in this field which could greatly benefit patients suffering from various diseases.

#### **Funding Support**

The authors declare that there is no funding support for this study.

#### **Conϐlict of Interest**

The authors reported the conflict of interest while performing this study to be nil.

#### **REFERENCES**

- Babiloni, F. 2010. From the Analysis of the Brain Images to the Study of Brain Networks Using Functional Connectivity and Multimodal Brain Signals. *Brain Topography*, 23(2):115–118.
- <span id="page-4-11"></span>Choudhari, S., Thenmozhi, M. S. 2016. Occurrence and Importance of Posterior Condylar Foramen. *Research Journal of Pharmacy and Technology*, 9(8):1083–1083.
- <span id="page-4-2"></span><span id="page-4-0"></span>deCharms, R. C., Blake, D. T., Merzenich, M. M. 1999. A multielectrode implant device for the cerebral

cortex. *Journal of Neuroscience Methods*, 93(1):27– 35.

- Edell, D. J., Toi, V. V., McNeil, V. M., Clark, L. D. 1992. Factors influencing the biocompatibility of insertable silicon microshafts in cerebral cortex. *IEEE Transactions on Biomedical Engineering*, 39(6):635–643.
- <span id="page-4-1"></span>Fernandez, E., *et al.* 2014. Acute human brain responses to intracortical microelectrode arrays: challenges and future prospects. *Frontiers in neuroengineering*, 7:24.
- <span id="page-4-10"></span>Gilley, P. M., Sharma, A., Dorman, M. F. 2008. Cortical reorganization in children with cochlear implants. *Brain Research*, 1239:56–65.
- <span id="page-4-12"></span>Gordon, K. A. 2011. Multiple effects of childhood deafness on cortical activity in children receiving bilateral cochlear implants simultaneously. *Clin*ical neurophysiology: official journal of the Inter*national Federation of Clinical Neurophysiology*, 122(4):823–833.
- <span id="page-4-13"></span>Gulino, M. 2019. Tissue response to neural implants: the use of model systems towards new design solutions of implantable microelectrodes. *Frontiers in neuroscience*, 13.
- <span id="page-4-8"></span>Hafeez, N., Thenmozhi 2016. Accessory foramen in the middle cranial fossa. *Research Journal of Pharmacy and Technology*, 9(11):1880.
- <span id="page-4-3"></span>Hassler, C., Boretius, T., Stieglitz, T. 2011. Polymers for neural implants. *Journal of Polymer Science Part B: Polymer Physics*, 49(1):18–33.
- <span id="page-4-7"></span>Hirano, S. 2000. Functional differentiation of the auditory association area in prelingually deaf subjects. *Auris Nasus Larynx*, 27(4):303–310.
- <span id="page-4-14"></span>Johnson, J. 2020. Computational identification of MiRNA-7110 from pulmonary arterial hypertension (PAH) ESTs: a new microRNA that links diabetes and PAH. *Hypertension research: official journal of the Japanese Society of Hypertension*, 43(4):360–362.
- <span id="page-4-6"></span>Kannan, R., Thenmozhi, M. S. 2016. Morphometric Study of Styloid Process and its Clinical Importance on Eagle's Syndrome. *Research Journal of Pharmacy and Technology*, 9(8):1137.
- <span id="page-4-4"></span>Keerthana, B., Thenmozhi, M. S. 2016. Occurrence of foramen of huschke and its clinical significance. *Research Journal of Pharmacy and Technology*, 9(11):1835.
- <span id="page-4-9"></span><span id="page-4-5"></span>Kipke, D. R. 2003. Silicon-substrate intracortical microelectrode arrays for long-term recording of neuronal spike activity in cerebral cortex. *IEEE transactions on neural systems and rehabilitation engineering*, 11:151–155.
- <span id="page-5-5"></span>Krishna, R. N., Babu, K. Y. 2016. Estimation of stature from physiognomic facial length and morphological facial length. *Research Journal of Pharmacy and Technology*, 9(11):2071.
- <span id="page-5-22"></span>Legris, E. 2018. Cortical reorganization after cochlear implantation for adults with single-sided deafness. *PloS one*, 13(9):204402.
- <span id="page-5-18"></span>Levine, S. P. 2000. A direct brain interface based on event-related potentials. *IEEE Engineering in Medicine and Biology Society*, 8(2):180–185.
- Mamelle, E., Kechai, N. E., Granger, B., Sterkers, O., Bochot, A., Agnely, F., Ferrary, E., Nguyen, Y. 2017. Effect of a liposomal hyaluronic acid gel loaded with dexamethasone in a guinea pig model after manual or motorized cochlear implantation. *European Archives of Oto-Rhino-Laryngology*, 274(2):729–736.
- <span id="page-5-15"></span>Maynard, E. M., Fernandez, E., Normann, R. A. 2000. A technique to prevent dural adhesions to chronically implanted microelectrode arrays. *Journal of Neuroscience Methods*, 97(2):93–101.
- <span id="page-5-10"></span>Menon, A., Thenmozhi, M. S. 2016. Correlation between thyroid function and obesity. *Research Journal of Pharmacy and Technology*, 9(10):1568.
- <span id="page-5-3"></span>Nandhini, J. S. T., Babu, K. Y., Mohanraj, K. G. 2018. Size, Shape, Prominence and Localization of Gerdy's Tubercle in Dry Human Tibial Bones. *Research Journal of Pharmacy and Technology*, 11(8):3604.
- <span id="page-5-1"></span>Normann, R. A. 1999. A neural interface for a cortical vision prosthesis. *Vision research*, 39(15):2577– 2587.
- <span id="page-5-2"></span>Pratha, A. A., Thenmozhi, M. S. 2016. A Study of Occurrence and Morphometric Analysis on Meningo Orbital Foramen. *Research Journal of Pharmacy and Technology*, 9(7):880.
- <span id="page-5-17"></span>Rousche, P. J., Pellinen, D. S., Pivin, D. P., Williams, J. C., Vetter, R. J., Kipke, D. R. 2001. Flexible polyimide-based intracortical electrode arrays with bioactive capability. *IEEE Transactions on Biomedical Engineering*, 48(3):361–371.
- <span id="page-5-23"></span>Ryu, S. B., Fried, S. I. 2018. Comparison of responses of visual cortical neurons in the mouse to intraocular and extraocular electric stimulation of the retina. *Annual International Conference of the IEEE Engineering in Medicine and Biology Society*, pages 2458–2461.
- <span id="page-5-11"></span>Samuel, A. R., Thenmozhi, M. S. 2015. Study of impaired vision due to Amblyopia. *Research Journal of Pharmacy and Technology*, 8(7):912.
- <span id="page-5-16"></span>Scherf, K. S., Sweeney, J. A., Luna, B. 2006. Brain Basis of Developmental Change in Visuospatial Work-

ing Memory. *Journal of Cognitive Neuroscience*, 18(7):1045–1058.

- <span id="page-5-14"></span>Schwartz, A. B. 2004. Cortical Neural Prosthetics. *Annual Review of Neuroscience*, 27:487–507.
- <span id="page-5-8"></span>Sekar, D. 2019. Methylation-dependent circulating microRNA 510 in preeclampsia patients. *Hypertension Research*, 42(10):1647–1648.
- <span id="page-5-9"></span>Seppan, P., Muhammed, I., Mohanraj, K. G., Lakshmanan, G., Premavathy, D., Muthu, S. J., Shimray, K. W., Sathyanathan, S. B. 2018. Therapeutic potential of Mucuna pruriens (Linn.) on ageing induced damage in dorsal nerve of the penis and its implication on erectile function: an experimental study using albino rats. *The Aging Male*, pages 1–14.
- Serruya, M. D., Hatsopoulos, N. G., Paninski, L., Fellows, M. R., Donoghue, J. P. 2002. Instant neural control of a movement signal. *Nature*, 416(6877):141–142.
- <span id="page-5-6"></span>Sriram, N., Thenmozhi, Yuvaraj, S. 2015. Effects of Mobile Phone Radiation on Brain: A questionnaire based study. *Research Journal of Pharmacy and Technology*, 8(7):867.
- <span id="page-5-12"></span>Stensaas, S. S., Stensaas, L. J. 1976. The reaction of the cerebral cortex to chronically implanted plastic needles. *Acta neuropathologica*, 35(3):187– 203.
- <span id="page-5-0"></span>Stensaas, S. S., Stensaas, L. J. 1978. Histopathological evaluation of materials implanted in the cerebral cortex. *Acta Neuropathologica*, 41(2):145–155.
- <span id="page-5-20"></span>Stropahl, M., Chen, L.-C., Debener, S. 2017. Cortical reorganization in postlingually deaf cochlear implant users: Intra-modal and cross-modal considerations. *Hearing Research*, 343:128–137.
- <span id="page-5-21"></span>Stropahl, M., Plotz, K., Schönfeld, R., Lenarz, T., Sandmann, P., Yovel, G., Vos, M. D., Debener, S. 2015. Cross-modal reorganization in cochlear implant users: Auditory cortex contributes to visual face processing. *NeuroImage*, 121:159–170.
- <span id="page-5-4"></span>Subashri, A., Thenmozhi, M. S. 2016. Occipital Emissary Foramina in Human Adult Skull and Their Clinical Implications. *Research Journal of Pharmacy and Technology*, 9(6):716.
- <span id="page-5-13"></span>Taylor, D. M., Tillery, S. I. H., Schwartz, A. B. 2002. Direct cortical control of 3D neuroprosthetic devices. *Science*, 296(5574):1829–1832.
- <span id="page-5-7"></span>Thejeswar, E. P., Thenmozhi, M. S. 2015. Educational Research-iPad System vs Textbook System. *Research Journal of Pharmacy and Technology*, 8(8):1158.
- <span id="page-5-19"></span>Torppa, R., Salo, E., Makkonen, T., Loimo, H., Pykäläinen, J., Lipsanen, J., Faulkner, A., Huotilainen, M.

2012. Cortical processing of musical sounds in children with Cochlear Implants. *Clinical Neurophysiology*, 123(10):1966–1979.

- <span id="page-6-0"></span>Vetter, R. J. 2004. Chronic neural recording using silicon-substrate microelectrode arrays implanted in cerebral cortex. *IEEE transactions on biomedical engineering*, 51(6):896–904.
- <span id="page-6-3"></span>Wartchow, K. M. 2020. Insulin-producing cells from mesenchymal stromal cells: Protection against cognitive impairment in diabetic rats depends upon implant site. *Life sciences*, 251:117587.
- Wellman, S. M. 2018. A materials roadmap to functional neural interface design. *Advanced functional materials*, 28(12):1701269.
- <span id="page-6-1"></span>Williams, J. C., Rennaker, R. L., Kipke, D. R. 1999. Long-term neural recording characteristics of wire microelectrode arrays implanted in cerebral cortex. *Brain Research Protocols*, 4(3):303–313.
- <span id="page-6-2"></span>Won, S. M. 2018. Recent Advances in Materials, Devices, and Systems for Neural Interfaces. *Advanced Materials*, 30(30):1800534.
- <span id="page-6-4"></span>Xie, H., Shek, C. H., Wang, Y., Chan, L. L. 2019. Effect of interphase gap duration and stimulus rate on threshold of visual cortical neurons in the rat. *2019 41st Annual International Conference of the IEEE Engineering in Medicine and Biology Society (EMBC)*, pages 1817–1820.