34th Annual International Conference of the IEEE EMBS
San Diego, California USA, 28 August - 1 September, 2012

Reliable Neural Interface: The first quarter century of the Neurotrophic Electrode

Phil Kennedy, MD, PhD, Neural Signals Inc., 3400 McClure Bridge Rd., Ste D402, Duluth GA 30096

Abstract

For development of a long-term, reliable cortical recording electrode, animal and human data support the approach of trapping the brain inside the electrode.

Introduction

The search for a reliable neural interface goes on though it should have ended some time ago. The purpose of the search is to provide long term neural control of prosthetic devices for communication, movement and speech. The history of electrode development has been to take what electrode works for acute recordings and develop these successful devices into chronic recording electrodes. Immense funds are being spent on achieving this aim by understanding the histological basis for rejecting these tine type electrodes and for developing new and more elaborate versions of tine type electrodes in the hope that longevity will appear. There is an alternative approach

Tyne type electrodes

These tine type electrodes depend on introducing a device into the brain hoping it won't be rejected and that it will record for the lifetime of the patient. The evidence for this hoped-for longevity is nowhere to be found. On the contrary, Cyberkinietics' evidence from human recordings is that the recorded units die off over years even though some simple functions can be derived from the few remaining units for over 1000 days or even longer [1]. The suggestion that these electrodes can be replaced after some years confirms the defeat of the longevity argument for these devices.

Alternative Approach

Instead of introducing the electrode into the brain why not introduce the brain into the electrode? This approach has been successful from the very beginning over a quarter century ago when the glass tip of a pipette was filled with autologous sciatic nerve and pushed into a rat's cortex [2]. Histological evidence showed that processes grew into and through the cavity thus anchoring the glass tip within the neuropil [3]. Next, a 3 mil gold wire, Teflon insulated, was glued inside the glass pipette tip using surgical glue (methacrylate) and this provided recordings of the ingrown tissue. Then two wires were introduced into the tip so that bipolar recordings could be isolated by the insulating glass cone from any extraneous interference, and comparison was made between each inside wire and an external wire. 42 rats were used to demonstrate that the clean multiunit recordings persisted as along as the rats persisted, a maximum of 16 months [2, 4]. Eight subsequent monkey implants demonstrated longevity of single unit recordings cut from the multi-unit steam until the moneys damaged the implants, as long as 15 months [5]. These recordings demonstrated movement related activity of sufficient quality that the FDA gave permission for human implants of the Neurotrophic Electrode, the first electrode to receive such permission.

Human Implants

Human implants began in 1996 with the aim of providing communication for locked-in subjects. The first subject (MH) demonstrated that the system would work though she died of her ALS complications before useful data could be obtained [6]. The next, (JR), became the world's first cyborg because he controlled a computer directly from his brain [7]. He showed that not only were single units useful, but he was the first to show that local field potentials could be useful controllers also [8]. His recordings continued over four years until he died of complications of his locked-in state. The next subject had such degenerative brain disease (mitochondrial myopathy) that even though his system endured for 4.5 years, his recordings were functionally useless. The fourth subject provided evidence that his signals were related to the few remaining EMG signals in his contralateral arm. By this time in the early 2000's, more evidence was forthcoming that non-invasive systems could provide communication, precluding the need to invade the brain to provide such communication. Thus the justification for invasive communication systems was difficult to make. Why not allow EMG and EEG systems to provide this slow communication pathway [9, 10, 11, 12]? For movement control, however, it seemed justifiable to use single units and local field potentials recorded intracortically or extracortically (ECOG). A different unique use for single unit recordings was sought. Thus was born the quest for the speech prosthetic, a prosthetic that would require a stable and reliable neural interface.

While the recognition of phonemes and single words has been made recently using ECOG recorded using cortical electrode arrays [13], the use of any type of EEG signal would appear to be insufficient for the fast decoding of neural signals required for rapid synthesis of speech if speech production rate is to be near conversational speed. The precision available from single unit firings has yet to be surpassed by any other method. The precision needed for control of robotic hands and digits in multiple dimensions is also believed to require single units [14, 15, 16]. Thus there are specific needs for a reliable neural interface that provides single units for the lifetime of the subject.

EVIDENCE SUMMARY

The evidence that the Neurotrophic Electrode can provide the necessary reliability and longevity comes not only from the animal recordings sited above but also from human recordings [6, 17, 18, 19, 20]. In the five human recordings, signals continued until termination (breakdown of the electronics or death of the subject) which was as long as 6 years in ER until electronic breakdown. When electronics are replaced the electrode(s) is (are) not replaced and signals continue once the new electronics are plugged in.

Signals have persisted for over four years in two subjects and 6 years in (ER) with recordings continuing until electronic breakdown. The number of single units remained the same for each subject over these time frames. The cluster cut parameter file that separates the single units is not changed once set. Many examples from studies in subject ER provide evidence for this point. (1) In the first study to identify phonemes, the cluster parameter file was not changed over the many months of recording that identified half the English phonemes [19]. After the electronics were first changed out in ER, the amplifier gains were slightly different and a new cluster cut parameter file was originated. (2) This new parameter file was not changed over the next half year of recordings where evidence was obtained for real time speech synthesis, a study in which ER had 80% success in producing four vowel phonemes using a center out task where the cursor is moved from a center phoneme to three outlying phonemes over a 2D formant frequency space with visual and auditory feedback [17, 18]. (3) In a study of singing performed over four years after implantation, the parameter file was again not changed throughout the months of recording. In this study [20], smooth firing rates of multiple single units gradually emerged both within sessions and across sessions over time, with final improvement occurring when feedback was provided whose volume was directly proportional to firing rate. In all these studies the same number of units was available, namely 31 units from a Neurotrophic Electrode containing three wires and attached to two implanted amplifiers. *There is no way that any of the progressive improvement in function could have occurred if units were unreliable.* Amplitudes remained the same, unit waveshapes remained the same, and the number of units remained the same [17, 18, 19, 20].

FUTURE DEVELOPMENTS

Despite these successes, the Neurotrophic Electrode undoubtedly needs improvement. It may have achieved reliability, but it has not achieved adequate numbers of units nor adequate spatial resolution. In other words, more units need to be recorded per electrode and per area of cortex. Towards this aim, a recent implantation of a monkey with two Neurotrophic Electrodes that contained six pairs of wires in each produced over 100 waveshapes (not yet defined as single units) [in progress]. Even though the ability to record more units per electrode is achievable with the presence of more recording wires, a preferred technique would be machined traces of gold viae on flexible substrates. In addition, the bulk of the tip precludes adequate spatial resolution. Therefore, smaller cone tips with multiple recording wires or viae are essential to improving the electrode. Using modern engineering tools and materials it should be possible to produce miniaturized cones with three dimensional recording sites that will surround the ingrowing neuropil and yet remain flexible and biocompatible. Such a configuration would allow stereotrode recording of the electrically active tissue and with multiple recording sites and would harvest an adequately large number of single units as well as providing local field potential recordings. Biocompatible materials are essential and the use of biocompatible glass, gold and Teflon may be superseded by other materials.

CONCLUSION

The take away message from these studies is not that the Neurotrophic Electrode as presently configured is optimal because clearly it is not, but rather that *growing the neuropil into the electrode is the key feature of any long lasting reliable recording cortical electrode*. Introducing foreign bodies into brains will only work if the brain can be induced to grow into the foreign body and remain trapped inside. *Trapping the brain inside the electrode is the key*. The data summarized above indicates that this approach works. Other approaches that do not incorporate this principle are likely to continue to fall short of the ultimate goal, namely, the lifetime recording of reliable neural control signals. The data summarized above suggest that the next quarter century of electrode development will be successful only if this principle is followed.

REFERENCES

1. Bacher D., Stavisky, SD, Simeral D, Donoghue JP, Hochberg LR. Use of a general purpose communication interface by an individual with tetraplegia in the brainGate2 clinical trial. *Society for Neuroscience Abstract* 899.8, San Diego, November 2010.
2. Kennedy P.R. A long-term electrode that records from neurites grown onto its recording surface. *J. Neuroscience Methods*, 29 (1989) 181-193.
3. Kennedy P.R., Mirra S and Bakay R.A.E.. The Cone Electrode: Ultrastructural Studies Following Long-Term Recording. *Neuroscience Letters*, 142:89-94, (1992).
4. Kennedy P.R., Bakay R.A.E. and Sharpe SAE. Behavioral correlates of action potentials recorded chronically inside the Cone Electrode. *NeuroReport,* 3:605-608, (1992).
5. Kennedy P.R. and Bakay R.A.E. Activity of single action potentials in monkey motor cortex during long-term task learning. *Brain Research* 760:251-4 (1997).
6. Kennedy P.R., Bakay R.A.E. Restoration of neural output from a paralyzed patient using a direct brain connection. *NeuroReport* 9,1707-11, 1998.
7. Kennedy PR, Bakay RAE, Adams K, Goldthwaite J, and M. Moore. Direct control of a computer from the human central nervous system. *IEEE Trans. Rehab. Eng.,* 8(2), 198-202, 2000.
8. Kennedy PR, Kirby MT, Moore MM, King B & Mallory A. Computer Control Using Human Cortical Local Field Potentials. *IEEE Trans on Neural Systems and Rehabilitation Eng*. 12(3), 339-344, 2004.
9. Wolpaw JR, McFarland DJ (2004) Control of a two-dimensional movement signal by a noninvasive brain-computer interface in humans. *Proc Natl Acad Sci USA* 101: 17849-17854.
10. Sellers EW, Krusienski DJ, McFarland DJ, Vaughan TM, Wolpaw JR (2006) A P300 event-related potential brain-computer interface (BCI): The effects of matrix size and interstimulus interval on performance. *Biol Psychol* 73:242-252.
11. Cheng M, Gao X, Gao S, Xu D (2002) Design and implementation of a brain-computer interface with high transfer rates. *IEEE Trans Biomed Eng* 49: 1181-1186.
12. Allison BZ, McFarland DJ, Schalk G, Zheng SD, Jackson MM, et al. (2008) Towards an Independent Brain - Computer Interface Using

Steady State Visual Evoked Potentials. *Clin Neurophysiol* 119: 399–408.

13. Pasley BN, David SV, Mesgarani N, Flinker A, Shamma SA, Crone NE, Knight R and Chang E. (2012) Reconstructing Speech from Human Auditory Cortex. *PLoS Biol* 10(1):e1001251.
14. **Velliste, M., Perel, S., Spalding, M. C., Whitford, A. S., and Schwartz, A. B.** (2008). Cortical control of a prosthetic arm for self-feeding. *Nature*, *453*(7198), 1098-1101.
15. Taylor DM, Tillery SI, Schwartz AB 2002 Direct cortical control of 3D neuroprosthetic devices *Science* 7 (296) 1829-32
16. Carmena JM, Lebedev MA, Crist RE, O'Doherty JE, Santucci DM, Dimitrov DF, Patil PG, Henriquez CS & Nicholelis MAL 2003 Learning to control a brain-machine interface for reaching and grasping by primates *PloS Biology* 1:2, 193
17. Guenther FH, Brumberg JS, Wright EJ, Nieto-Castanon A, Tourville JA, Panko M, Law R, Siebert SA, Bartels JL, Andreasen DS, Ehirim P, Mao H, Kennedy PR. A wireless brain-machine interface for real-time speech synthesis. *PLoS One*. 2009 Dec 9;4(12):e8218.
18. Brumberg JS, Nieto-Castanon A, Kennedy PR, Guenther FH. Brain-Computer Interfaces for Speech Communication. *Speech Commun*. 2010 Apr 1;52(4):367-379.
19. Brumberg J., Wright EJ, Andersen D, Guenther FH and Kennedy PR. Classification of intended phoneme production from chronic intracortical microelectrode recordings in speech motor cortex. *Frontiers in Neuroscience* 5(65) 2011.
20. Kennedy, P.R., Andreasen D.S., Bartels' J., Ehirim P., Mao H., Velliste M.,Wichmann T.,Wright, E.J. (2011) Making the lifetime connection between brain and machine for restoring and enhancing function. *Proceedings in Brain Research* August 2011.