Chapter 4

Neural Recording Using Digital Telemetry

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Abstract

Digital telemetry (DT) offers a method of collecting the electrical signals produced by neural activity and transmitting them wirelessly to a receiver/decoder for analysis and storage. The wirelessness means that activity can be recorded from a subject that is behaving relatively normally, which opens up a number of research and therapeutic opportunities – for example, in the study of spatial encoding, or in pre-seizure activity in an epileptic subject. In this chapter we first review the history of neural recording and describe the classic analog method of data processing, outlining the technical problems that need to be solved in collecting and transmitting tiny electrical signals within a noisy environment. We then outline digital signal processing together with the basic principles of telemetry, describing how DT solves these problems in a way that preserves signal fidelity while allowing subjects to move around in an unconstrained way. We finish by describing several situations in which DT is enabling advances to occur both in the laboratory and in the clinic.

Key words: Single-unit, Neuronal ensemble, Freely moving, Wireless, Analog, Digital signal processing, Epilepsy, Clinical study, Spatial correlate, Cognition

1. Introduction

A major aim in neuroscience is to determine what information is being encoded by ongoing neural activity by recording the activity and then, in essence, decoding it. This enterprise is rooted in the assumption that the collective activity of individual neurons encodes biologically meaningful signals including sensations, perceptions and actions, and also more subjective mental phenomena like feelings, memories, and thoughts and it has two main aims. On the one hand, deciphering the "neural code" (or rather codes) will advance the intellectual endeavor of understanding how the brain works. On the other hand, sufficiently accurate decoding has enormous potential to advance clinical practice,

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especially the treatment of neurological disorders and mental dysfunction for which treatment options often depend on rapid and accurate diagnosis.

Recording meaningful signals from the brain's vast panoply of neurons is a far from trivial technological enterprise. Because many areas of the brain are simultaneously active, and because large neural networks often encode information, it is often necessary to record from hundreds of neurons simultaneously in order to determine the kind of information being processed, and the way in which this processing occurs. Animal studies of high-level knowledge structures such as the "cognitive map" (1) benefit from ensemble recordings of large numbers of neurons made using arrays of electrodes. Clinically, our best current guess is that decoding discrete events like an impending seizure, specific aberrant feelings, and bizarrely inappropriate thoughts will require the ability to record the simultaneous ensemble action potential activity of many thousands of neurons. Furthermore, several decades of research have revealed that the brain has a mostly modular organization and so it is necessary not only to be able to record the signals, but also to be able to determine, with a reasonable degree of accuracy, their anatomical source. And finally, for sophisticated animal experiments, and also for clinical use in humans, it is necessary that these recordings be undertaken not in an anaesthetized and immobile preparation but in an awake and preferably ambulatory subject. These three requirements – high bandwidth, anatomical localization, and portability – pose enormous challenges for the designers of neural recording systems.

Recent years have seen significant advances in technologies for decoding brain signals. Field potential recordings, such as 12-channel EEG, provided early electrophysiologists with a means to record pre-ictal or frank seizure activity in epileptic patients, while intracranial recordings, undertaken before or during surgery, have provided neurosurgeons with the ability to determine seizure foci with a high degree of precision. More recently, brain imaging techniques like functional magnetic resonance imaging and optical tomography, which can detect the global metabolic activity of particular brain regions, have been able to pinpoint the source of brain activity with resolution as precise as 1 mm. However, neither the spatial nor temporal resolutions of such methods can yet match the spatial and temporal scales of individual neurons and their action potentials. These technologies have been, to date, clearly limited in their bandwidth, their anatomical precision, or their portability.

Electrophysiological single-neuron recordings will be central to the decoding effort described above because of their high anatomical specificity, and also because electrical signals are lightning fast events that can be immediately captured and which provide high-resolution information about neural activity changes.

Furthermore, electrical signals can be recorded from sites that are up to several tens (or even hundreds) of microns distant from the recording electrode, allowing collection of information from multitudes of simultaneously active neurons.

Such high-speed data collection necessitates high-speed processing power. This has become increasingly feasible over the past decade, where advances in digital signal processing (DSP) technology have made it possible to process vastly more data than before using increasingly more compact recording systems. Whereas an early single-neuron recording system would typically occupy a large 19-in. rack standing in the corner of a laboratory or operating theatre and provide only a few channels of data, requiring a large computer for collection and off-line analysis, modern systems offering more than 100 channels can be as small as a laptop computer and, indeed, require only a laptop for processing. It can safely be assumed that further miniaturization will continue to make recording systems increasingly compact and high bandwidth, thus meeting two of the three criteria for clinical and research utility.

What about the third criterion – that of portability? A compact multi-channel single-neuron recording system is undoubtedly better than a large one, but if the subject needs to be tethered to it by a recording cable then the range of laboratory experiments is highly constrained, and clinical utility remains limited to the bedside. Increasingly, however, scientists would like to record from behaving subjects in real-world settings, and clinicians would like to be able to record from ambulatory patients, either during routine daily-life monitoring or in emergency situations in the field. Although acquiring and storing data with a subject-mounted memory device may be an option in some cases, the ideal solution to the tethering problem would be to devise a means of wirelessly transmitting multi-channel neuronal data at high speed. Recent developments in wireless signal transmission, in the form of wireless digital telemetry (DT), are beginning to make this possible. In the present chapter we review the principles of DT recording, and then describe a DT device that we have developed that we think has the capacity to advance both basic research and clinical practice.

The digital telemeter is fundamentally an inexpensive, miniature, battery-operated, multi-channel, portable digital system to record wideband bioelectric signals. DT can be designed to record both fast and slow brain potentials such as action potentials (APs; 0.3–6 kHz) and local field potentials (LFPs). Its digital technological nature makes it ideally suited to the introduction of a radio link, which obviates the need for wires between the subject and the data-storage machine. DT can be made inexpensive and small because it exploits the billion-dollar market for portable audio applications, which drives chip manufacturers to perfect these

circuits by continuously reducing noise, power consumption, size, and price while increasing fidelity. DT measures biopotentials with high precision because it digitizes signals on the subject at high (e.g. 24-bit) resolution. The signals are immune to electromagnetic distortion because digitized data are transmitted in an interference-resistant, error-correcting, wireless digital protocol.

Below, we first briefly outline the history of single-neuron recording in behaving subjects, before reviewing the conventional analog strategy and then the DT strategy for making these recordings. Then we focus on the technical features that are now attainable with DT technology, including the capacity to multiplex and wirelessly transmit high-bandwidth signals between subject and recording system. Finally, we will briefly consider three application scenarios in which DT has been deployed.

1.1. Historical Overview

Single-unit recording from the brains of freely-behaving subjects began in the late 1960s with the use of implanted microwires to collect extracellular action potential signals, coupled with field-effect transistors (FETs) placed close to the electrode on the animal's head, to provide the first stage of processing. James Ranck Jr., a key innovator of the extracellular technique in behaving animals, has recounted the history of single-unit recording in the context of hippocampal place cell studies (2). We provide a very selective and brief version of the story we have learned from Ranck.

Single-neuron recordings in freely-behaving subjects have always, to date, relied on extracellular techniques because intracellular recordings (such as are used in brain slices) are impractical due to the tremendous mechanical difficulty of impaling a neuron and then maintaining the delicate intracellular connection on a moving subject for the duration of behaviorally-relevant episodes. Extracellular recording does not depend on charge transfer between the brain and electrode, instead measuring the electric field that is created by extracellular current flow. The voltage at the electrode conductor depends on the strength of the field and thus the proximity of the electrode to the field source. This capacitive voltage is typically small, on the order of a few hundred microvolts, meaning that recording systems need to be sensitive, and also that electrical noise poses a significant challenge.

Single mammalian central neurons were recorded from the hippocampus of the anesthetized cat a full quarter century before FETs enabled recordings from freely-moving animals (3). In those days, signals were recorded as varying analog voltages on an oscilloscope. Throughout the 1950s, single neurons were recorded using glass microelectrodes with fine tips, which are advantageous for getting close to neurons with minimal damage to other parts of the brain, but which have very high impedance. High electrode impedance (Z_e) causes several major problems for recording the small single-unit

potentials that are picked up by extracellular electrodes. The signal is attenuated by the relative magnitude of the amplifier input impedance (Z_a) according to the ratio $Z_a/(Z_a+Z_c)$. The electromagnetic noise pickup is a positive function of signal impedance in the cable that connects the animal to the amplifier. Perhaps most ruinous is "movement artifact," in which moving the recording cable causes microphonic noise, which arises from multiple sources, including the piezoelectric and triboelectric effects, and which is also a positive function of signal impedance.

In 1957, Hubel used sharpened tungsten for extracellular recordings of single neurons in the anesthetized cat (4). Tungsten is more robust than glass but it is still fragile. The next year Strumwasser showed that single neurons could be recorded with cut 25 μm insulated wire (5). Unlike tungsten, the cut-wire electrode was not brittle, allowing it to withstand the violence of head movements. Olds used the cut-wires to record from awake rats (6), but to get useful recordings he had to train the rats to remain motionless because the impedance of 25-μm cut-wires is still large (about 1 MΩ).

Everything changed in the late 1960s when FETs became available that were both small and resistant to failure. Able to be mounted on an animal's head, the FET made it possible to record extracellular action potentials from single neurons in freely-moving subjects by lowering the signal impedance directly at the connection to the electrode. The much reduced impedance in the cable from the animal to the recording system meant that movement artifact was substantially attenuated and recordings could be made in normally-behaving and locomoting subjects. Using this method, O'Keefe was able to observe that neurons in the hippocampus are spatially selective (7), thus igniting the study of internal high-level cognitive structures in the brain.

Extracellular recording technology has come a long way since FETs were first introduced, and measurements made by eye from oscilloscope traces, but most recording systems are still fundamentally analog, with a digital stage that is remote from the subject. Electrode signals are initially subjected to a number of operations such as amplification and filtering for frequency bands of interest. Only when all such pre-processing has been completed are the signals sampled and digitized for storage and display on a computer. In analog systems, therefore, the main advance in recording technology has been to replace the conventional oscilloscope by a software counterpart running on a computer.

The analog processing still used in most conventional recording systems is in contrast with many other types of instrumentation, and virtually all consumer electronic devices, which these days are fully digital. In digital devices, the original analog signals are converted to a string of binary numbers early in the signal pathway and all the subsequent processing, such as filtering, are

done numerically, in software. The digital telemetry concept described in this chapter applies these techniques of early digitizing and digital signal processing to the processing of electrophysiological signals. Even ignoring its "wirelessness," the DT approach thus departs in important ways from the conventional recording strategy. Below, we detail each step in the processing pathway, describing the conventional method for achieving such processing and then comparing this with DT.

2. Steps in the Recording Process: Conventional Analog Vs. DT Systems

The new DT technology described here offers advantages over conventional recording systems at each step of the process from the signal in the subject's brain to the computer. Electrophysiological signals from mobile subjects are processed via the following steps (Fig. 1): Collection of the signal, buffering, digitization, amplification/filtering, and transmission to the data acquisition system. A major difference between conventional analog recording and DT is that the steps typically take place in a different sequence (though this is not essential) – whereas in analog recordings the signal is first buffered, then transmitted, then amplified and filtered, and finally digitized, in DT the buffering, amplification, and digitization all occur locally, on the subject, and then the digitized signal is multiplexed (to convert the multiple channels of data to a single stream of binary digits) before being sent by radio link to the recording system. This process is detailed in the next section.

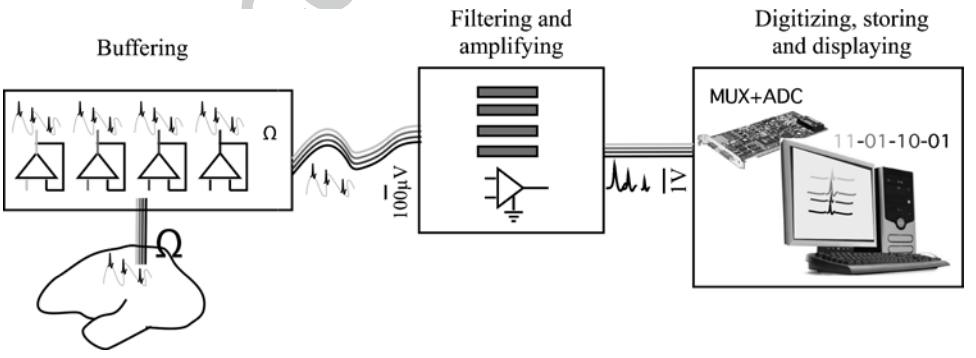

Fig. 1. Different stages of a conventional recording system. Simultaneous local field (LFP) and action potential (AP) signals are detected with high-impedance electrodes and buffered to reduce the signal impedance. The wideband signals from each electrode are transmitted by a galvanic conductor to an amplifier for band-pass filtering and amplification (~10 K gain). Here the scheme depicts that the AP frequency band (300–6,000 Hz) has been selected and the LFP signal is lost. The filtered signal is now ~1 V and relatively immune to electromagnetic interference. The signal from each amplifier is sent to an analog-to-digital converter (ADC) where it is digitized (typically at 12–16 bits resolution), stored, and/or displayed under computer control.

2.1. Signal Collection and Buffering

In modern-day extracellular recording systems, neuronal signals are collected by intracerebral high-impedance, fine microelectrodes, configured either singly or in bundles, and usually comprising either insulated microwires (e.g. ceramic-coated 25 µm platinum–iridium alloy) or silicon probes. The first buffering stage of processing usually takes place on the subject, as close to the electrode connector as possible. Operational amplifier integrated circuits that incorporate large numbers of FETs in convenient packages are used for signal buffering. Although the signal amplitudes are typically small (for example, action potentials are a few hundred microvolts and local field potentials are about 1 mV), the primary purpose of this stage is to reduce the impedance of the signal, which is typically a few hundred kiloohms and depends on the properties of the electrode. Reducing impedance ensures that the source impedance is lower than the impedance of the amplifier, which allows the signals to be relatively immune to electromagnetic noise and movement artifact. Remarkably, clinical EEG systems, and many animal EEG systems, do not use a buffering stage, or if they do it is not until the vulnerable signals have traveled up through a few meters of unbuffered wire. This is a major reason that EEG recordings in animals and patients are artifact-prone. Buffering at the electrode interface allows field and action potentials as small as 40 µV to be recorded from freely-moving rats – even while the animals are jumping or being dropped (8, 9). In DT, buffering does not occur as a separate stage but is part of the signal-conditioning process that takes place prior to transmission (Fig. 2).

2.2. Filtering and Amplifying

Neural signals, which are tiny voltages of the order of tens or hundreds of microvolts, need to be amplified, and they also need to be filtered to remove noise and to isolate the frequencies of interest. In a conventional system, amplification and filtering take place after the signal has been transmitted to the recording system, as described later. This means that any distortion of the signal that occurs en route is amplified along with the signal itself. If the signal can be filtered and amplified on the rat, as in the case of the DT, the amplified signal is far more resistant to subsequent transmission distortion. (It is also the case that because digitization has taken place on the rat too, as we describe later, even more robustness is added to the signal.)

Amplifiers are typically used in a differential configuration, in which a reference signal from an electrode implanted elsewhere in the brain is subtracted from the signal of interest in an effort to remove unwanted signals that are common to both electrodes, such as electrical mains noise ("common-mode rejection"; see Fig. 3). Signals are also typically AC-coupled to remove DC potentials. In our DT, the electrode signals are fed to a differential instrumentation amplifier. As with conventional systems,

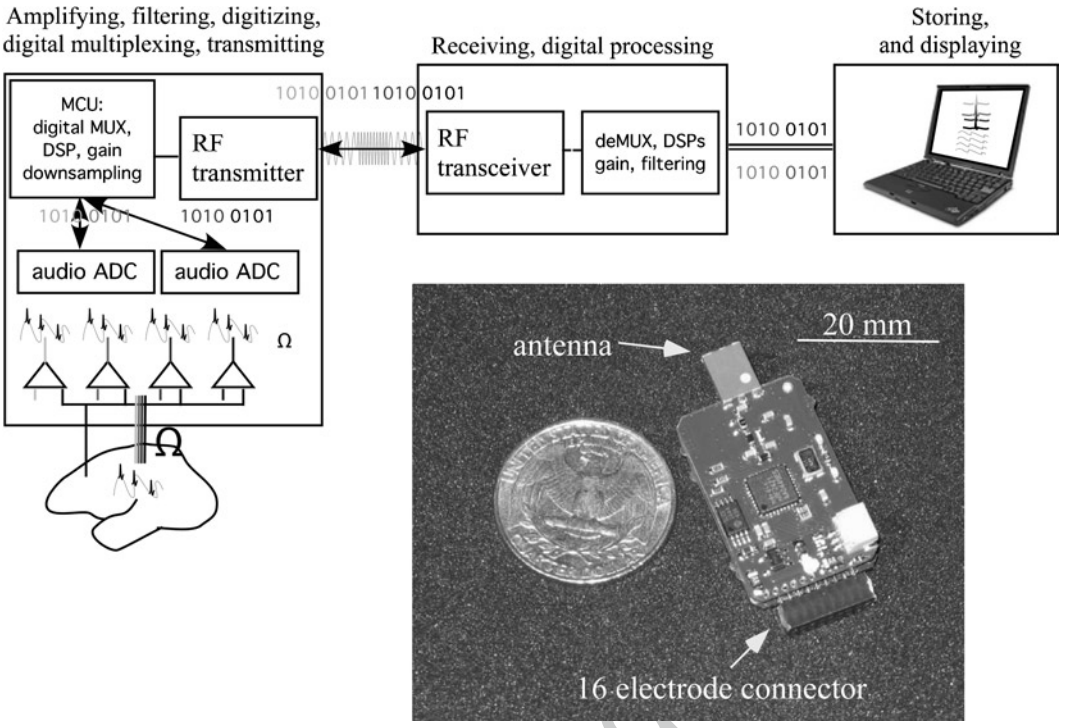

Fig. 2. Stages of our DT recording system. Simultaneous LFP and AP signals at high-impedance electrodes are amplified five times, and the common mode interference from an indifferent electrode (*black*) is subtracted in the amplifying stage, which also reduces the signal impedance. The wide-band output from pairs of amplifiers is low-pass (<6 kHz) filtered and digitized by an audio delta–sigma ADC that digitizes and combines the data from two electrodes in a standard digital audio data format. The binary digital data signal is now a few volts and relatively immune to electromagnetic interference. The outputs from a set of ADCs are combined into one digital signal by digital multiplexing (MUX). Only two ADCs are depicted in the schematic, but any number can be used so long as the aggregate digital data streams can be managed by the next stage of digital signal processing. The digital data are processed (filtered, reordered, multiplied, ignored, etc.) by a microcontroller unit (MCU). The processed digital signal is fed to a radio transceiver integrated circuit and transmitted as a frequency-modulated 2.4 GHz radio signal. A remote receiver converts the radio signal to a digital signal and the data are reorganized into separate stereo data streams conforming to a digital audio standard by an MCU within the receiver. The digital audio stereo signals are processed by digital signal processing (DSP) units, which can filter the data into any band for storage and display under computer control via the USB. Both AP and LFP signals from each electrode can be captured. (*Inset*) A photograph of a DT transmitter stage.

a signal from a reference electrode is subtracted to remove common-mode noise, and a small amount of gain (200–300×) is applied.

The function of subsequent filtering is to remove unwanted frequencies in the signal so that the frequencies of interest can be analyzed separately. Action potential waveforms, because of the sharp nature of their waveforms, have high-frequency components between 300 Hz and 6 kHz and conventionally require high-pass filtering so that the slow undulations of the EEG can be removed. By contrast, local field potentials (LFPs) such as hippocampal sharp wave-associated ripples (10, 11) tend to have maximum frequencies of about 300 Hz, and normally are

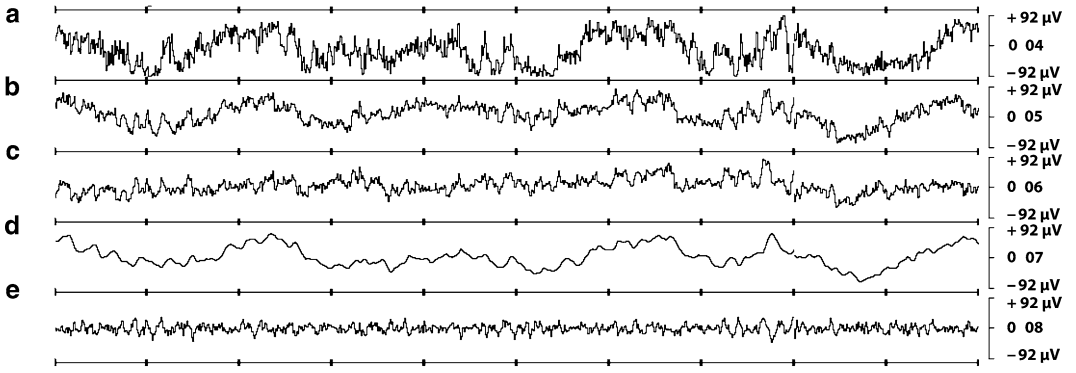

Fig. 3. Effects of filtering on a rat brain signal recorded with HM-L-coated 25 µm platinum–iridium wires. (**a**) The raw, unfiltered, and unreferenced signal. (**b**) Effect of referencing: the same signal after a signal from a nearby wire has been subtracted from it, removing the common mode noise. (**c**) The referenced signal after application of a 50 Hz notch filter to remove mains noise. (**d**) The referenced and notch filtered signal after being low-pass filtered (1–250 Hz). Note that the slow undulations persist but the highfrequency, spiky elements have been removed. (**e**) The referenced signal after being high-pass filtered. Notice that the low-frequency undulations have been removed but the spiky, high-frequency elements remain: these are due to background neural and other electrical activities. Traces recorded on an Axona DacqUSB system by Robin Hayman.

high-pass filtered so that the superimposed AP spikes can be removed (Fig. 3). This is necessary in conventional systems due to the limited resolution at which signals are digitized. By contrast, DT allows both high- and low-frequency signals, from APs and LFPs, respectively, to be recorded simultaneously. This is because the DT digitizes the signal at a very high resolution, as described in the next section. This has a number of advantages, one of which is that DT requires only minimal filtering (specifically, only the input AC-coupling plus a simple two-pole anti-alias filter before the digitization stage).

Analog filters, such as the commonly used Butterworth-type, work by reducing the amplitude of those components of the signal that are outside the frequencies of interest, with the attenuation gradually increasing for signals further from the filter's passband. For a typical filter design, if the high-pass frequency is set to 6 kHz, the amplitude of signal components at 12 kHz may only be reduced by 60%, thus leaving a considerable residue of high-frequency signal energy. Thus, it would be necessary to sample such a signal at a rate much higher than 12 kHz, even though the highest frequency of interest is only 6 kHz. In principle, it should only be necessary to sample a signal at two times the highest frequency of interest (the so-called Nyquist limit).

2.3. Digitization

Digitization involves taking the continuous, time-varying voltage signal produced by neurons and converting it to a stream of numerical values that can be subjected to analysis in software. In conventional analog recording systems, digitization takes place

right at the end of the signal processing pathway, after the signal has been transmitted from the subject to the recording apparatus. The reason that wireless recording of single neurons has become feasible in recent times is that miniaturized digital signal processing (DSP) chips have become available that are so small that the digitizing can take place on the subject itself, rather than in the recording system. This offers a number of advantages. Perhaps the most important of these is that, for reasons described in the next section, digital signals can be more reliably transmitted from the subject to the rest of the recording system. The signal is thus highly immune to movement artifact or electrical noise that might otherwise be introduced in the transmission pathway.

In converting a continuous and smoothly varying signal into a discrete set of samples, digitization causes a loss of information in the spaces between the samples; it introduces constraints on resolution both vertically (i.e. in the amplitude domain) and horizontally (in the time domain). In the amplitude domain, the number of bits used to encode the signal amplitude constrains how fine-grained the amplitude representation can be, which can be problematic if both the high-amplitude (mV) LFP signal and the low-amplitude (μV) AP signal are simultaneously of interest. For example, hippocampal 4–12 Hz, θ oscillations (11) tend to have 1 mV amplitudes, and large irregular activity (LIA) is several millivolts, nearly two orders of magnitude greater than APs (11).

While many investigators avoid this problem by focusing on only one or the other signal-type, in recent years there has been a substantial interest in studying the relationship between concurrent LFP (population) and AP (single cell) signals because it seems that this relationship may be used to encode information (12–16). Thus, the problem of how to simultaneously record both high-amplitude LFPs and low-amplitude APs needs to be solved.

In conventional analog recording systems, digitizing takes place right at the end of the processing sequence, and is usually done by PC-based analog-to-digital converters (ADCs). By this stage the signal has already been magnified, and the frequencies of interest isolated, by analog components, as described in the section on amplification and filtering. Although there are PC-based 16-bit ADC cards, commercial ADCs that operate at above 1 MHz (allowing 32 AP channels to be digitized at 32 kHz) typically operate at 12-bit resolution. To maximize the resolving power of the ADC, the frequency band for the signal of interest is selected in the filtering stage and then amplified to utilize most of the bits in the digitization stage. In conventional systems, this can be done by setting the gain so that signal peaks do not saturate the ADC; the result of this is that on average, the signal is represented by up to 4 bits less than the maximum resolution of the ADC, effectively reducing the resolution of a 12-bit ADC to only 8 bits. Since LFP amplitudes are greater than AP amplitudes

by an order of magnitude, only the low-frequency LFP band or the high-frequency AP band can be digitized with sufficient resolution, but not both. Consequently, to record both the LFP and the AP bands from one electrode requires doubling the number of main amplifiers and ADC channels, so that the signal can be processed in parallel, in both ways.

An alternative approach, rather than filtering the signal two different ways, is to use the capability of modern ADCs to sample the signal at vastly higher resolution. In our DT, the ADCs digitize at 18–24 bits, which – even with minimal amplification of the input signal – allows for a wide dynamic range: this means that both APs in the microvolt range and large LFPs in the millivolt range are able to be captured simultaneously from the one signal.

In the time domain, digitization also produces problems when a continuously varying signal is sampled at discrete time intervals because a problem known as aliasing arises (Fig. 4), whereby the undersampling of high-frequency components in the signal introduces spurious additional low-frequency components, and/or a shift in phase of some components. Given the likely importance of phase in neural encoding, this is obviously a serious problem and so it is necessary to avoid aliasing by making sure that the signal is sampled at a frequency at least twice that of the highest frequency in the input (the Nyquist limit previously alluded to). For neural signals, digitization is usually done at a rate of about 32 kHz/channel for action potential data, while local field potentials are digitized at 1 kHz or less. As discussed in the section on filtering and amplification, the highest frequency of interest even in APs is around 6 kHz, so that it should only be necessary to sample at 12 kHz, but the limitations on conventional

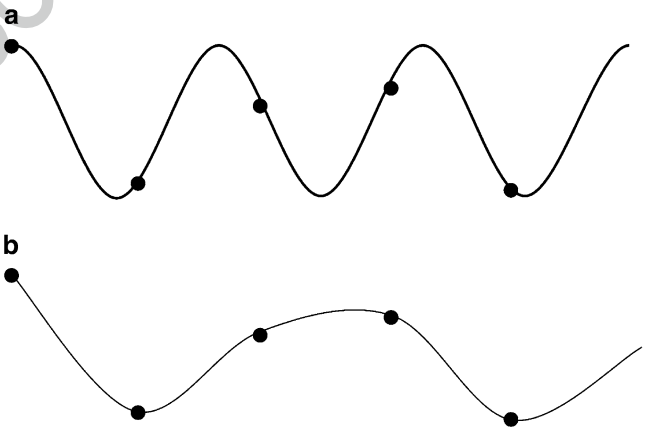

Fig. 4. Aliasing caused by undersampling of a signal. (**a**) The original signal is a regular sine wave of constant peak amplitude. The dots show the points at which samples were taken. (**b**) When a curve is reconstructed from the samples, using interpolation to fill in the spaces, the reconstructed signal is distorted in frequency, phase, and amplitude relative to the original.

filters to attenuate frequency components above 6 kHz quickly enough require that a much higher sampling rate be used.

An alternative is to use almost no filtering, but sample the signal at a very high frequency, so that only very high-frequency signals (tens to hundreds of kHz) are at risk of being aliased back into the brain signal frequency band (17). However, very high rate digitization brings with it a number of problems. As we describe later, our implementation of DT instead uses a particular kind of ADC (delta–sigma), which has a very high "internal" sampling rate, but an easier-to-work-with output sample rate. This allows us to have to a very simple filter, but nevertheless to sample at only 12 kHz, exactly twice the 6 kHz highest frequency of interest.

2.4. Transmission to the Data Acquisition System

The next step in the signal-processing sequence is to transmit the data from the animal to the data acquisition system for further processing. This process faces two challenges. First, the signal needs to maintain integrity (e.g. preserved signal-to-noise ratio) over the often meters-long distance between the animal and the recording system. Second, the medium of signal transmission – usually wires, in the case of a conventional system – places limitations on the amount of data that can be carried. For example, to collect many channels of data simultaneously in a conventional system, it is necessary to run at least as many wires from the subject to the recording system as there are electrode channels, which limits the number of channels that can be recorded at once due to the weight of the cabling (especially for small subjects like rats and mice). It also forces the subject to be "tethered" and thus restricted to a relatively small spatial area. While tethered recordings have been (and continue to be) enormously useful, they limit the kinds of investigations that can be conducted.

Multiplexing the signals can alleviate the tethering problem, which involves combining the multi-channel data into a single channel that can be transmitted via just one wire for demultiplexing by the recording system. An alternative, or additional solution, is radio transmission of the signal, which eliminates the need for heavy cabling but which renders the signal potentially vulnerable to electromagnetic interference.

Multiplexing can be used with both analog and digital signals, and with either wired or wireless signal transmission. The signals from multiple channels are broken up into short fragments which are spliced together into a single signal, transmitted to the recording system and then demultiplexed into individual channels again at the other end. This introduces data loss in the temporal domain for each channel due to the time needed to transmit the remaining channels. For analog demultiplexing, the signals from each channel are sampled and held as voltages by capacitors during the intervals while the remaining channels are being transmitted.

This means that the amplitude of the signals can continue to be rendered with high resolution, but because they are being held by capacitors, which naturally leak over time, they are inherently less accurate. With digital signals, a similar fragmenting and splicing process occurs, but demultiplexing is electronically simpler because the data stream was, and continues to be, a string of bits (with signals represented by large discrete voltage levels) rather than a smoothly-varying voltage.

The signal then needs to be transmitted to the recording system. Multiplexing greatly reduces the need for multiple wires between the subject and the recording system: for example, our DT multiplexes the signals from 16 channels onto one wire, and needs only two more wires for power and ground, making three in total. However, the number of wires can be reduced to zero by transmitting the information as a radio signal.

Radio transmission of neural signals was originated decades ago (a review by (18)), and an early device was even capable of transmitting single-unit signals (19). The natural place to insert a wireless link is just after the buffering stage. In a conventional analog recording system, this is usually done by taking the buffered analog voltages, multiplexing them as described above, and using the multiplexed signal to modulate a radio frequency carrier wave. The original signals are recovered at the receiver by demodulating the received radio signal and demultiplexing the signal back into the individual channels comprising it. This is "analog telemetry." In principle, this carrier-wave modulation could even be used to transmit multiple unmultiplexed signals in the same way that continuous stereophonic audio signals are mixed into a single wave, and then separated again at the receiving end. In practice, this is very complicated to achieve for multiple signals, and multiplexing is preferred, even with the slight data loss it entails.

Radio signal transmission has the problem that the signal between the transmitter and receiver is vulnerable to distortion or fading. As the distance between the transmitter and receiver varies, the received signal strength varies as well, and at larger distances the signal may drop below the level at which it can be successfully received, causing data loss. Since the radio signal is transmitted at a single frequency, reflections of the signal in the recording environment can interfere destructively with the original signal, causing reception to fail. Furthermore, other sources of radio interference can affect reception, such as wireless telephones and networks, computers with wireless peripherals, microwave ovens, engines, etc.

These problems are serious with analog systems because once the signal has been corrupted it cannot be recovered, and it is impossible to know that such corruption has occurred. By contrast, digital signals can be protected by means of error detection/correction

algorithms (detailed below) which enable the received signal to be checked for error. If these occur, the receiver can request the retransmission of data "packets" (stored locally on the subject after digitization). Thus, radio transmission of digital data – digital telemetry – offers the great advantage that data can be collected in a robust and high fidelity manner without the impediment of recording cables.

Our DT wireless transmission exploits a radio transmitter integrated circuit that was originally intended for the consumer digital audio market. This device offers a number of features that make it particularly attractive. It is small (15 × 15 mm total circuit area including all components) and low-powered, which is important for a portable battery-operated device, particularly if it is to be carried by a small animal. It accepts and transmits standard audio-format signals, but also provides a parallel bi-directional data channel that can be used to communicate between the transmitter's built-in miniature microcontroller unit (MCU) and the recording system. And most importantly, it offers various mechanisms for overcoming radio frequency (RF) noise, reflections, and other problems that might threaten the transmission of acquired electrode data. It does this by sacrificing more than half of its native 4 Mb/s radio link bandwidth to "Quality of Service" (QoS) protocols – in particular, it packages up the sampled electrode data and attaches "checksums," which are essentially periodic summaries of the foregoing data stream, that are transmitted along with it. If the signal is corrupted in-air, the received checksum will no longer match its corresponding data stream and so the receiver will request a retransmission. Furthermore, both transmitter and receiver are able to dynamically change their operating frequency ("frequency hop") to optimize radio link reliability. Even in cluttered lab environments where other wireless networking components are often present, the device is able to work at several meters' range, often out of line-of-sight, without any radio link dropouts.

3. A Specific Implementation of DT

In the foregoing sections, we have outlined the general characteristics of conventional neuronal recording systems, and hinted at particular ways in which the digital telemetric approach we have developed can improve upon this conventional approach. For the past several years we have been utilizing emerging DSP and telemetry technology to design a DT that specifically enables high-speed transmission of many channels of single-neuron data. In this section, we describe a specific implementation of DT, discussing particular choices of components and configurations and the

Table 1 t1.1
A summary table of our DT technical specifications t1.2

Feature	Value	
Data rate	1.536 Mb/s	t1.4
Analog/digital conversion	18–24 bits	t1.5
Max voltage resolution	1–38 nV/bit (at gain = 200)	t1.6
Input range	± 5 mV (at gain = 200)	t1.7
Bandwidth	0.64–6 kHz (at 12 kHz ADC)	t1.8
Crosstalk	90 dB	t1.9
Noise level	1 μVpp	t1.10
Input impedance	1.0e12 Ω	t1.11
CMRR	115 dB	t1.12
Current consumption	80 mA	t1.13

reasons for these, together with an evaluation of performance of the DT. The technical specifications are summarized in Table 1.

3.1. Description of DT

As previously described, our DT implementation integrates signal buffering, differential recording, filtering, amplification, digitizing, multiplexing, and a radio transmission stage into one tiny unit. The buffering and differential referencing is accomplished by high-precision instrumentation amplifiers at the DT's inputs. Signals are then AC-coupled (0.05 Hz highpass). Minimal amplification (200–300×) is necessary, since the digitization stage utilizes a 24-bit ADC and so can resolve down to 1 nV per bit (or 38 nV/bit with an 18-bit ADC).

In order to avoid aliasing problems but still be able to sample at the Nyquist limit, we use a particular kind of analog-to-digital converter, the "delta–sigma"-type, which offers several advantages. At 12 kHz digitization, the delta–sigma ADC has a linear-phase anti-aliasing filter that attenuates frequencies between 5.8 and 6.0 kHz by 70–90 dB. The linear phase property means that the introduced phase-shift changes linearly within the passband. This is unlike the standard Butterworth-type filter that is used in most conventional analog main amplifiers. The filter roll-off is very steep (approx. 70 dB/octave) meaning that frequencies near 12 kHz are attenuated by about 3.5 orders of magnitude. This sharp roll-off allows DT to sample 6 kHz signals (APs) at 12 kHz without aliasing. A second feature of the delta–sigma ADC which supports this is that by internally oversampling the signal (by an order of 100 times the output sample rate) it allows the DT's

output sample rate to approach the Nyquist limit. This means that high-frequency APs can be safely digitized at a rate that is a fraction of the conventional recording system data rate, dramatically reducing the bandwidth required to transmit the signals and the space required to store them.

3.2. Bandwidth Usage Optimization

As discussed previously, the native bandwidth of our DT's radio transmitter is 4 Mb/s. After application of the QoS mechanisms that guarantee robust signal transmission, the device offers a residual bandwidth of 1.536 Mb/s for the actual data to be carried. The actual contents of this data stream are not constrained by the radio device, which allows us to use the DT's MCU to structure them in a large variety of ways. The MCU contains timing circuits, which allow the sampling rates of the ADCs to be under software control. Since the MCU receives the digitized data streams from the ADCs, it can reorganize these in a wide variety of ways; specific channels can be selected for amplification, downsampling, and transmission, while others are ignored. Again, this selection process is fully programmable. Finally, the MCU can choose how many of the ADCs' native bits of resolution are actually kept (i.e. it can transmit only the top 8 or top 12, or 16 as necessary). This constellation of features allows combinations of different numbers of channels at different sampling rates and resolutions to be processed and transmitted.

Since the bandwidth available to any radio communications device has some limit, this ability of the DT to have its data stream configured for purpose on the fly allows it to optimize the use of the available bandwidth. For example, in a situation where more electrodes have been implanted than the radio would have bandwidth to transmit at a high sample rate, an experimenter can select those electrodes with the best signals, and transmit only those. Alternatively, it might be preferable to transmit more signals simultaneously, but at lower resolution.

3.3. Power Management

In order to operate completely wirelessly, a DT requires an independent source of power. Typically, this will be a rechargeable battery, carried either on a head-mounted device for short recordings and/or on a larger subject, or on the animal's back for longer recordings on a small animal such as a rat or mouse. A battery weighing only 3.5 g is sufficient to power the DT for 1.5 h.

However, an alternative for animal studies might be to locate an electromagnetic power source under the animal's cage, and use inductive pickup within the DT transmitter to extract power from the surrounding electric field as in inductively-coupled power transfer (ICPT) technology. In principle, such an approach can suffer from the problem of what to do to control the power level; excessive induced power would need to be dissipated as heat, which could be problematic. However, the DT's radio link

allows it to establish a feedback connection over the air with the inductive power source and instruct it to maintain appropriate output levels. Thus, DT can be the basis for a continuous recording system.

3.4. Testing DT

To compare DT rigorously with conventional analog recording, we used a test signal with the waveshape properties of a continuous burst of APs (high-frequency peaks at 3,555 and 5,587 Hz and peak amplitudes ~105 μV; interspike interval 3.5 ms). The first thing to note is that the DT-recorded waveform properties were superior to those measured from a commercial analog recording system having 12-bit digitization (Fig. 5). The voltage recorded at the sample that most often contained the peak voltage was much more variable in the analog system. The coefficient of variation was 40% compared to only 11% with DT. Even though the analog system is digitized at 32 kHz, and the DT at 12 kHz, this result illustrates that DT more reliably captured the peak of the AP-like signal. This is a property of the delta–sigma-modulated ADC in DT. Waveform properties can be more accurately calculated by reconstructing the signal from the digitized values. Even so, parameter estimates from cubic spline reconstructions of the DT recordings were less variable than the spline estimates from the conventional analog recordings.

Note also that the waveform properties were virtually identical when recorded by DT via galvanic and radio transmission. This occurs because the transmitted signal is digital and thus not subject to distortion. Either the signal is transmitted faithfully, or there is a dropout. If a bit is lost and cannot be recovered by error correction the whole signal is lost until the reading frame of the formatted bit stream is recovered. 99.7% of the signals were

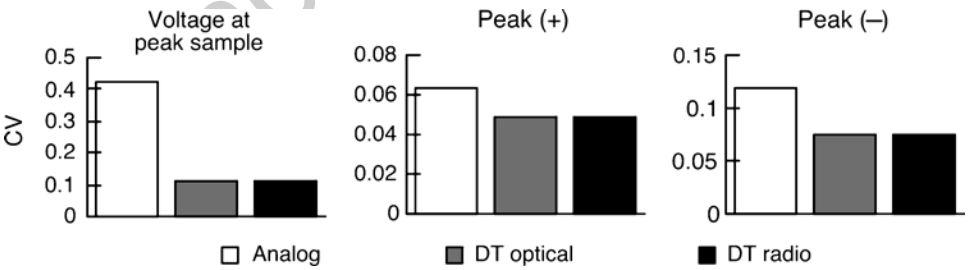

Fig. 5. Waveform properties recorded by an analog 12-bit system, and DT with galvanic and radio transmission. Since the gains and filtering in the analog (10,000 times, 300–6,000 Hz) and DT (100 times, 50–6,000 Hz) systems differed, the coefficients of variation (CV) for three waveform properties are plotted. The voltage at peak sample describes the voltage at the ADC sample, which was most often the largest voltage. This parameter describes how well the rapidly changing peak voltage was sampled. Oversampling by the delta–sigma-modulated ADC in DT measured the peak more reliably. This digitization error can be attenuated by reconstructing the continuous waveform from digitized values. A cubic spline was used to represent the continuous waveform, and the positive and negative peaks from the spline function were calculated. The variability of peaks in the DT waveforms was still smaller. Waveforms were identical for galvanic and radio transmission.

transmitted wirelessly as the experimenter moved within 10 m of the receiver without regard for maintaining line-of-sight between the transmitter and the receiver. Transmission did not degrade when competing radio frequency interference was produced by Wi–Fi transmission from either a wireless Ethernet router or laptop placed 1 m from the receiver. These simple tests demonstrate that the DT's radio communication is robust.

4. Practical Uses of DT

As discussed earlier, the great advantage of DT is that it frees the subject from the constraints of a recording cable, allowing recording of neuronal activity in far more behaviorally relevant settings (see Fig. 6). It greatly enhances the ability to record from the brain. So far there are three broad domains in which such technology is proving to be particularly useful: experiments in animal epilepsy, animal cognition studies, and clinical use.

4.1. Animal Epilepsy Monitoring

Epilepsy is a devastating disorder and anti-convulsants are often limited in efficacy or have intolerable side effects. Surgical intervention is an undesirable last resort that is not even always possible. Therefore, rapid progress in understanding epilepsy depends on use of animal models to develop new approaches to treatment or even cures. Detailed observations and therapeutic assessments that are initially not clinically possible can be performed in animals. However, in the animal as well as in the clinical setting, it is difficult to correlate electrographic and behavioral seizure manifestations, necessitating continuous video monitoring and analysis.

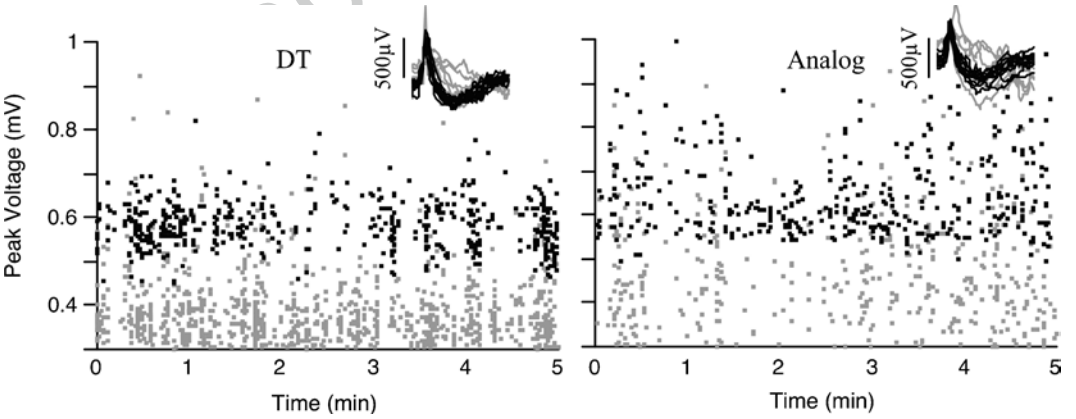

Fig. 6. DT offers improved discrimination even at the input stage. The digital signal was converted to analog and recorded by a commercial analog system for 5 min then the electrode was recorded by the conventional system. Plotting peak action potential voltage against time reveals that the discriminated unit (*black*) is less variable. The unit was also more distinct from other APs (*gray*) in the DT recording (i.e. the peak was more separate from other events).

Furthermore, seizures in animals, as in humans, may manifest electrographically but not be accompanied by overt behavioral signs. This means that epilepsy research needs chronic, 24-h EEG in order to test potential anti-convulsant therapies with accuracy. In addition, to understand mechanisms, the high-frequency (80–500 Hz) oscillations and other aspects of the EEG may be important clues that a seizure is about to occur. Current technology is limiting because it involves low-resolution recordings of only the lowest frequencies (<70 Hz), and animals must be attached to cables for recordings outside their home cage. DT, being inexpensive, miniature, wireless, and portable, has the potential to solve many of these issues. Accordingly, we have merged DT and digital video technologies (20) to create what we call the animal Epilepsy Monitoring Unit (aEMU) to permit standardized, video-synchronized, continuous wideband, multi-site electrophysiological recording in the rat home cage. This enables the study of the prediction, treatment, and basic science of spontaneous seizures in animal models of epilepsy.

In clinical epilepsy, the Epilepsy Monitoring Unit (EMU) has enormous diagnostic and therapeutic utility. It is used for identifying seizure type and severity, monitoring therapeutic efficacy, and determining the targets for surgical intervention. Given the centrality of the modern EMU, not only in clinical practice but in the development of our current understanding of epilepsy, it is remarkable that there are currently few comparable systems for animal experimentation that permit such long-term (days to weeks) recordings. In addition to direct consequences for epilepsy research, the lack of an EMU has indirect consequences – only the models with the most obvious and severe motor convulsions are typically studied. Less obvious seizure-manifestations cannot be studied easily. Thus technical limitations preclude the more direct study of the human disease.

Current animal monitoring protocols that do use EEG have additional problems. Animals usually require transportation to a remote chamber, pressure to the head to connect cables, and tethering of the head for recording: these can be substantial stressors. Stress can exacerbate seizures and alter their manifestation (21, 22). Stress to the head can cause irritation or pain, disturb electrodes, and lead to problems that confound the assessment of seizures. DT recordings, however, allow an animal to move in its home cage uninfluenced by experimenters, providing accurate estimates of epilepsy-related events with reduced stress.

DT is ideally suited to investigate the electrical origins of spontaneous seizures and the mechanisms of epilepsy. The focus of most epilepsy research has been on field potentials (0.5–500 Hz). The wideband abilities of DT will also make it easy for researchers to investigate whether information about seizure development and evolution is also contained in the fast AP activity of

single-unit ensembles of individual neurons, or in their spatio-temporal relationships to field potentials. As discussed earlier, the relationship of spike discharge of individual neurons to LFPs is intensely investigated in several areas of neuroscience. One of these is concerned with understanding the organization and balance of excitation and inhibition (23, 24). Excitation/inhibition imbalance has long been a central hypothesis for seizure genesis, but these spike-firing patterns have not been investigated due to bandwidth restrictions and to the restricted numbers of available channels. The aEMU will permit study of these unit/field relations. High-frequency oscillations are now also suspected to be a key aspect of epilepsy and epileptogenesis (25). Current animal EEG systems do not provide the signal-to-noise ratio or bandwidth required to detect these small events (~100 μV; ~10% the amplitude of slower oscillations), which the high voltage and temporal resolutions of DT is readily able to detect.

Figure 7 shows a photograph of a rat with a DT transmitter for continuous recordings in its home cage. The rat has epilepsy, which DT was crucial in discovering. The rat received an ibotenic acid lesion as a 7-day-old pup, which is a widely used preparation to create animals with schizophrenia-related characteristics (26). In some of these animals, we noticed what might have been mild seizure-like events that were very brief, lasting 2–3 s. Subsequent, chronic monitoring using DT revealed that these animals were indeed having spontaneous seizures that occurred every day or so. These electrographic seizures were often not accompanied by overt behavioral manifestations. Since schizophrenia researchers typically observe one of these animals only for a few tens of minutes, it is not surprising that epilepsy has not been reported in these animals. However, this provides a clear illustration of how use of DT can advance and refine investigations into the neurobiology of epilepsy and other neurological and mental dysfunctions.

4.2. Animal Cognition Studies

A second major potential use for DT is in neurobiological studies of animal cognition. Early studies of animal behavior focused on simple behaviors such as reinforcement learning and perceptual discrimination, exemplified by the early and influential School of Behaviorism, which ignored (or even denied) the existence of internal knowledge structures such as the "cognitive map." However, as the field has advanced, scientists have become increasingly interested in such cognitive structures, particularly as the development of chronic single-neuron recording made the demonstration of these structures indisputable. The consequent rise of "Cognitivism" has meant that behavioral studies have become increasingly sophisticated, and it is becoming necessary to increase the sophistication of recording systems to match. DSP technology has made possible the recording of many neurons simultaneously, and now DT makes this possible in subjects that are behaving in situations that approximate natural conditions.

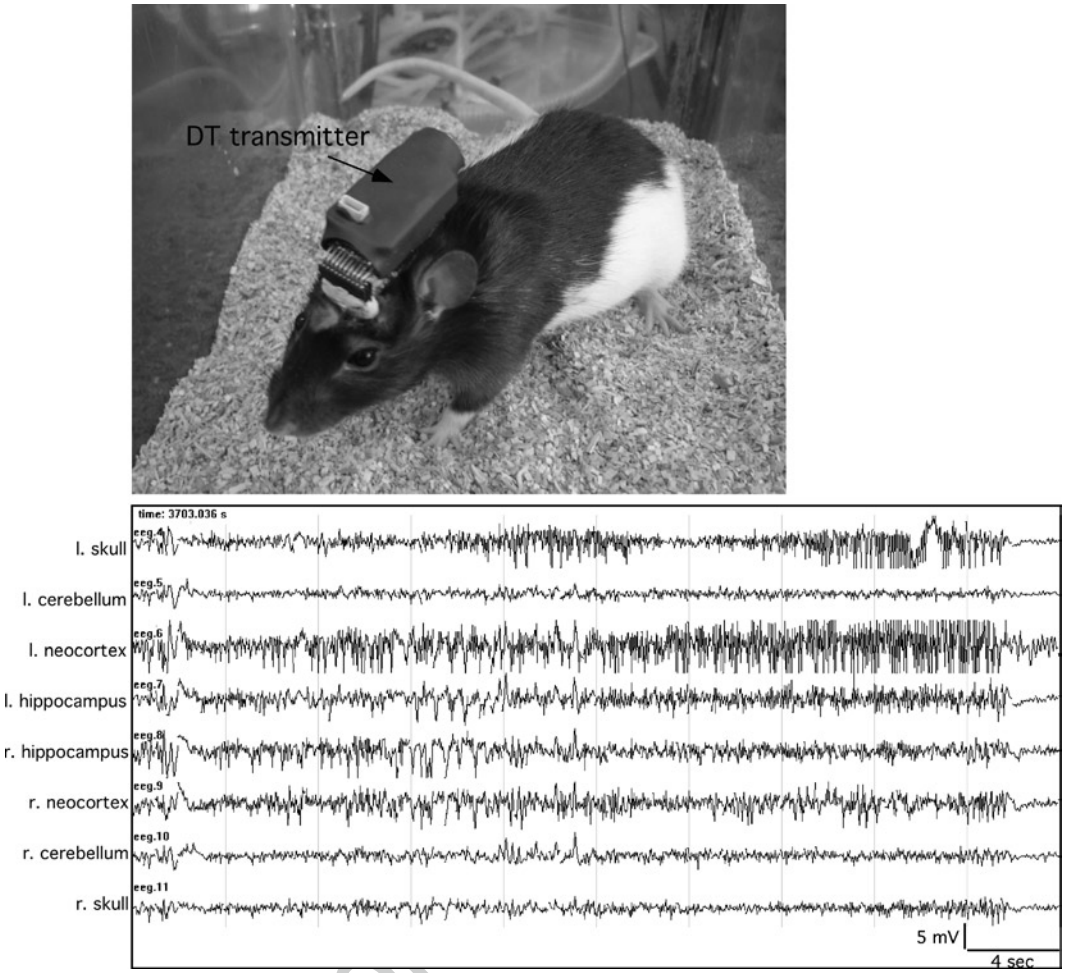

Fig. 7. (*Top*) Photograph of a rat wearing a DT transmitter in its home cage for chronic recordings. In this configuration, with power supplied to the transmitter electronics wirelessly by magnetic induction and wireless radio transmission to a remote receiver, an animal can be recorded continuously for arbitrarily long periods of study. This is especially valuable for monitoring spontaneous events that are rare, like electrographic seizures in animal models of epilepsy. (*Bottom*) Forty-second traces from an eight-channel DT recording of a spontaneous, generalized seizure in an adult rat that received a ventral hippocampal excitotoxic insult as a 7-day-old neonate. The voltage traces are local field potentials at eight locations indicated to the left of each trace. Chronic DT recordings were used to discover that these animals have approximately one spontaneous seizure per day. This seizure frequency is considered low by experimental criteria but high by clinical criteria. Furthermore, this neonatal lesion preparation is not an established epilepsy model; it is, however, closely related to a well-established developmental model of schizophrenia (26). Seizures in this model have not been reported, probably because of the low seizure frequency and the corresponding need for chronic monitoring to detect seizure events (recordings by Hsin-Yi Kao and Heekyung Lee).

One of the areas in which this technology promises to be most useful is in spatial behavior, in which animals traverse large regions of the environment in order to solve a spatial task such as navigating to a goal or returning home from a foraging expedition. With tethered recording systems it has been possible to build up a picture of how neurons represent small, two-dimensional spaces;

of course, space is not two-dimensional, it is three-dimensional, and naturally-behaving animals will typically move considerable distances vertically as well as horizontally in their daily lives – when, for example, climbing through burrow systems or trees.

The study of spatial encoding in large or complex environments is only just a beginning, but initial results suggest that this field of enquiry is poised to take off in the next few years. Already such studies are revealing aspects of the neural representation of space that were not appreciated by recordings from standard, small experimental spaces. One example is the grid-cells, recently discovered in the medial entorhinal cortex. These cells discharge in multiple, regularly spaced locations that tile an environment in a hexagonal grid pattern of spatial action-potential discharge (27). Although the grid pattern is striking, it was not initially recognized in recordings from medial entorhinal cortex as rats explored standard experimental spaces of about 1 m (28–31). More recently, these authors have reported data from very extended 18-m long environments (32) – an enormous technical challenge when the subject is tethered to a recording cable. Another experiment in a large-scale space recorded place neurons from the hippocampus as rats explored a 1.4 × 1.5 m chamber, finding that place fields became multiple, in a pattern that had never been recognized in recordings from small environments (8). Thus, recordings while rats explored larger than typical environments have corrected our notions of the fundamental firing pattern of cells in the hippocampus and medial entorhinal cortex. It is certain that such experiments are just the beginning of our attempts to understand representation in large-scale space, but further development of this line of enquiry will require telemetry. DT will make it possible, for the first time, to record in (relatively) more naturalistic settings such as vivarium colonies or three-dimensional mazes. Such recordings will rapidly permit us to build up a picture of how neurons in different brain areas are naturally active during normal daily behaviors such as social interaction, foraging, mating, nest-building, rearing of offspring, and fighting with intruders.

4.3. DT in Clinical Settings

As well as advancing animal studies, DT also promises to substantially advance clinical electrophysiology applications. While many applications are envisaged, perhaps the most obvious is seizure monitoring in epileptic patients from scalp and intracranial electrodes. Specific properties of DT, especially the high digital resolution and range, wideband frequency response, small size, portability, and battery-power converge to enable, also for the first time, recording APs and LFPs from the brains of freely-moving people. Such recordings can be accomplished before, during, and after seizure, with good chances of maintaining stable detection of the same set of neurons and neuronal potentials. Human intracranial recordings have not typically been made using buffering amplifiers at the electrode connectors because of

their large size, mechanical coupling to large batteries, and heat generation, which made it impractical to store such equipment under the wound bandages on the subject's head. Instead, the buffering amplifiers have been located at the level of the subject's chest and unbuffered wires that carry the high impedance signals from the electrodes make the connection. As a result, changing electric fields in the vicinity of the subject induces noise currents in the unbuffered pathway and this prevents recordings during movement, seizure, and even after seizure when clinical staff is attending to the patient. Since DT is miniature and low-powered, it can be placed under a bandage with only a lead from the battery carried somewhere on the subject's person. DT digitizes at the electrode interface and transmits the digital signal without wires, so these problems are avoided and recordings that were previously impossible become straightforward. As an enabling technology, DT has substantial potential within the next decade to establish whether high-frequency LFPs and AP spike trains from single and multi-unit intracranial recordings have clinical utility for diagnosing neurological and psychiatric disorders (33, 34).

5. Conclusion

This chapter has reviewed the principles of chronic single-neuron recording and introduced the new technology of digital telemetry. Neither digital signal processing nor telemetric transmission are new; what is new is the use of recently developed high-speed DSPs and ADCs to enable digitization and processing of multiple, high-bandwidth neuronal channels locally, at the source (i.e. on the subject). This means that digitized single-neuron data, which are much more robust to degradation and are also more easily processed than its analog counterpart, can be feasibly transmitted by radio link in a way that has never been possible previously. This, in turn, opens the door to new types of recording scenarios which we have detailed in the final section; such scenarios include recording in complex environments where a cable would become entangled or prolonged recording in clinical situations where a human subject does not wish to be tethered for long periods of time.

What is next for telemetric neuronal recording? Since chip technology continues to evolve at a rapid rate, it is likely that it will soon be possible to record from many more channels simultaneously, meaning that truly large-scale ensemble neuronal recording will finally be possible. Currently, one of the biggest limitations in technology is the need for a power source to be carried by the subject. Since battery life is a universal problem in modern electronic applications, battery technology is intensively researched for the consumer market and so it is likely that the advent of miniature, long-lasting high-capacity rechargeable batteries will

eventually mean that prolonged neuronal recordings can be undertaken even on rodents. This is an exciting possibility, for it means that truly naturalistic studies of neuronal activity, in which neurons are recorded over long periods of time as animals live their daily lives without experimenter intrusion, will become possible. If the range can be extended, and combined with GPS localization technology, it may even become possible to record neuronal activity from animals in the wild – for example, from navigating or even migrating animals. On the clinical side, it may mean that the development of indwelling neural pacemakers (i.e. long-term implanted electrodes that detect abnormal neural activity and then correct it) will at last become feasible. It seems likely that in the not-so-distant future, recording cables will be regarded as a quaint and archaic feature of old-fashioned recording systems, and the next generation of neurophysiologists will wonder how this one ever managed to do any experiments at all!

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