IV CONCLUSIONS

19 The Next Ten Years and Beyond

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The brain is arguably one of the most complex systems ever studied by science. Major insights and constraints about brain function can be obtained from lesion studies as well as behavioral studies (Finger, 2000). Yet, ultimately, a mechanistic understanding of the computations that underlie cognition requires speaking and interpreting the language of the brain: spikes (Rieke et al., 1997; Kreiman, 2004; Koch, 2005). To understand how our cognition is implemented, we need to investigate the human brain from the inside.

Significant advances in our characterization of neurons and neuronal circuits came about with the advent of techniques to "listen to" spikes (Adrian, 1926; Hubel & Wiesel, 1998). Most of the efforts to examine the activity of neurons have focused on studies in animal models given the difficulties inherent in invasive studies of the human brain. Yet, even from the early days of neurophysiology, neurosurgeons became interested in exploring neuronal function in the human brain (see chapters 2 and 3).

Earlier chapters have documented the potential and insights derived from recording neuronal activity in the human brain in a variety of domains. Invasive studies of the human brain can transform our understanding of human cognition at a mechanistic level and can also help us better understand and treat neurological disorders including epilepsy, Parkinson's disease, Alzheimer's disease, and other cognitive and motor disorders.

Here we would like to suggest possible areas of investigation in the field that may provide significant insights during the next decade and beyond. While many of the discussion here will take a speculative tone, we hope that these notes will help inspire the next generation of researchers to push the frontiers of knowledge. The discussion here does not aim to be exhaustive in any way: We hope to be at least partly wrong and be surprised by exciting new unforeseen discoveries. We somewhat arbitrarily divide these future directions into ten different but overlapping themes.

Learning and Memory, Time Travel

Many of the depth electrode cases in epileptic patients target the medial temporal lobe (MTL) including the hippocampus and surrounding structures. These regions provide a unique

opportunity to further our understanding of the neuronal circuits and mechanisms that underlie learning and the conversion of short-term to long-term memories (see chapters 7–9).

Studying the human brain can provide glimpses into aspects of episodic memory that are not easily amenable to exploration in animal models. It has been argued that sophisticated forms of episodic memory are unique to humans and can thus only be studied in humans (Tulving, 2002; Hampton & Schwartz, 2004). Different timescales of memory formation have been described at the neuronal level; it will be interesting and important to examine whether and how these different temporal scales are encoded in MTL neurons. Work in rodents has largely focused on spatial learning. It is conceivable that these spatial navigation studies constitute an example of a more generic mechanism for associations. Further strengthening the links between rodent/macaque neurophysiological studies and human studies can prove fruitful to investigators working with all models.

It has remained very difficult to directly link the mechanisms of synaptic plasticity to memories (Martin et al., 2000). This is in part due to the difficulty of testing for the presence of a memory without being able to directly query subjects on the content of their memory. Human experiments offer the unique opportunity to make a contribution toward our understanding of which neuronal mechanisms support memories. This is particularly the case for remote memories (Frankland & Bontempi, 2005; Squire & Bayley, 2007). We are able to recall memories that were established years or even decades ago, but the processes by which such remote call works remain largely unknown. Furthermore, our ability to imagine ourselves in a future scenario and time travel into an imagined future may also be dependent on MTL machinery (Nyberg et al., 2010; Addis et al., 2011). Thus, working at the single neuron level with human patients who can time travel from their distant past into a potential future and report their experiences can provide rare insights into these uniquely human conditions.

Work with human patients offers the opportunity to directly query subjects about memories form many years ago. Additionally, emotions are likely to play a key role in memory formation (chapter 13; Cahill et al., 1995; Fanselow & Gale, 2003; Phelps, 2004). The relationship between emotional processing and memory formation has been only poorly studied in the human brain (see discussion below).

Recently, a few studies have suggested that it may be possible to enhance memory formation through electrical stimulation of sites in the MTL or sites outside the temporal lobe sites connected to it (Laxton et al., 2010; Suthana et al., 2012) or through pharmacological interventions (Bentley et al., 2011). Future studies are needed to further our understanding of how such interventions work to enhance learning and memory.

Emotions

Another area within the MTL that is often targeted in depth electrode implantation cases is the amygdala. Significant evidence from lesion studies and animal studies suggests that this large

structure plays a critical role in processing emotions (see chapter 13). Certain aspects of emotional processing have been examined in animal models, particularly using behavioral paradigms such as fear conditioning. The repertoire and depth of emotions that can be studied in animal models is limited. The study of emotions constitutes a prime example where single neuron recordings in the human brain can lead us to uncover a representation that is extremely difficult to investigate with other methods and models. Important initial steps in this direction were described in chapter 13.

The amygdala is a very large structure; at the anatomical level it is composed of multiple different nuclei. Some of these nuclei are distinct in terms of their input and output. It is tempting to speculate that these different nuclei will manifest differential responses to different aspects of emotional processing, a topic that has received little attention. The large repertoire of emotions that humans are sensitive to has seen only preliminary investigations and deserves further scrutiny. Perhaps there exists a functional subdivision of different types of emotions encoded in different substructures, although this is an admittedly oversimplified hypothesis.

There is a significant overlap in the patient population between autism spectrum disorders (ASDs) and epilepsy. A behavioral hallmark of ASD involves difficulties in social interactions including interpreting and expressing emotions. It has proven remarkably difficult to identify animal models that express the behavioral anomalies of ASD patients. Investigating the neurophysiological properties of neurons in the amygdala in ASD patients can yield significant advances toward a mechanistic understanding of the elusive nature of ASD.

Additionally the role of the amygdala in posttraumatic stress disorder has been a topic of considerable investigation (Ursano et al., 2010). Studies in the human amygdala using recording and stimulation paradigms may add invaluable data with potential implications for the treatment of this disorder.

Language and Communication

Beyond memory and emotions, several aspects of cognitive science lend themselves to investigation in humans. One such example is language (e.g., see chapter 14). Language, at least in the forms typically discussed within the cognitive science literature, is specific to humans. Temporal dynamics play a central role in language generation and understanding, making it difficult to study with techniques that have poor spatial and/or temporal resolution.

Uncovering the neural code underlying language is particularly difficult as there is no good animal neurophysiology to build upon. Recent work by Tankus et al. (2012) reports on a highly structured neuronal encoding of vowel articulation. In medial–frontal neurons, highly specific tuning to individual vowels was found, whereas in superior temporal gyrus, neurons had nonspecific, sinusoidally modulated tuning (analogous to motor cortical directional tuning). At the neuronal population level, a decoding analysis revealed that the underlying structure of vowel encoding corresponded to the anatomical basis of articulatory movements. This structured

encoding enabled accurate decoding of volitional speech segments and could thus potentially be applied in the development of brain–machine interfaces for restoring speech in paralyzed individuals (Tankus et al., 2012).

Another example involves the extrapolation of mirror neurons from nonhuman primates to humans. Indeed, single neuron work may shed light on this system, which appears to be quite spread out in human cortex (Mukamel et al., 2010).

Free Will

A particularly intriguing aspect of decision making involves those situations where choices are made volitionally as opposed to being triggered by external inputs. We have a strong subjective feeling that we are free agents owning our destinies. The notion of free will has been debated for millennia and is at the heart of our very essence of *self* (Haggard, 2008). Our legal system is based on the assumption of the existence of free will (Cashmore, 2010). Our daily actions depend on how we interpret free will. Yet, ultimately, our volitional decisions must be encoded by neurons in our brains. When, how, and with which neurons volitional decisions are orchestrated remains a daunting and elusive problem (see initial steps and discussion in chapter 8). Intriguing and heroic efforts have been made to characterize neuronal signatures preceding volitional movements in animal models, but it remains quite difficult to interpret the animals' notion of self and will. How free will relates to different brain structures has received significant attention in neurological studies as well as noninvasive scalp EEG studies (e.g., the *Bereitschaftspotential* and its modulations). In comparison, there has been minimal work at the neuronal circuit level in the human brain. Experiments in humans (Fried et al., 1991; Fried et al., 2011) offer a unique opportunity to interrogate the neuronal circuits and mechanisms underlying free will because tasks can be designed in which subjects make voluntary decisions and because we can control external variables and have some degree of access to subjective decisions. An intriguing question involves whether there is a "point of no return" in voluntary decisions. In a rather simplistic model, one could conceive of a hierarchical chain of commands ranging from the initial will all the way to the implementation at the level of motor neurons and muscles. What aspects or processes within this dynamical chain can be interrupted and which ones cannot be interrupted may shed light on the elusive and fascinating circuitry that can implement the most capricious of cognitive phenomena. Experimental paradigms that utilize real-time processing to visualize internal thought processes are powerful tools that will likely be instrumental in teasing apart the architecture of voluntary decisions (see chapters 6 and 8).

Consciousness

Free will is but one aspect of the general problem of finding the neuronal correlates of consciousness (chapters 8 and 11 in this volume; Koch, 2005). The study of animal models has made tremendous contributions to help formulate questions about how the contents of consciousness

are represented in a rigorous fashion amenable to scientific investigation. At the same time, the lack of subjective reports leads to restricting ourselves to experimental paradigms that require careful quantification of behavior and extensive training. While we certainly need to continue with experiments in animal models, there is always the lingering question about the extent to which animals solve the tasks in the same way that we do or experience the same sensations upon presentation of the same stimulus.

Human neurophysiological recordings can provide a bridge between noninvasive measurements in humans and more invasive studies in animal models. So far, this field has been largely focusing on experiments that parallel research efforts in animal models. Experiments have been conducted in which the same stimulus in some cases leads to conscious experience and in other instances doesn't (e.g., binocular rivalry; see chapter 8). Investigators then correlate single neuron activity with conscious experience. Multiple (speculative) discussions about the representation of consciousness have argued that consciousness is the consequence of interactions between multiple brain areas. These putative interactions have been poorly explored in human neurophysiology. While in some cases, the small number of electrodes and limited sampling might make it difficult to systematically examine such interactions, it still seems that examining interactions across units, or coherence between unit activity and local field potential (LFP) activity in different areas (e.g., Womelsdorf et al., 2007) and coupled with subjective report of conscious human subjects, may provide unique insights.

Sleep

Overnight recordings offer a rich data set that allows investigators to delve into the fascinating and often-mysterious patterns of brain activity during sleep (see chapter 10). Many efforts have centered on characterizing firing rates, synchronization, and other activity patterns during each of the different sleep stages and during events defined by large-scale recordings such as spindles or K-complexes.

A fascinating and largely unexplored aspect of sleep involves dreams. Recently, a functional imaging study took initial steps in an effort to decode brain activity during dreams (Horikawa et al., 2013). While the elusive nature of dreams has always made them difficult to study, one would hope that the resolution of single unit studies may shed light on how neurons represent the contents of dreams. Furthering our understanding of brain activity during dreams may have important implications not only for addressing this age-old dilemma but also for elucidating the neural correlates of consciousness and memory recall.

There is ample evidence that multiple tasks show sleep-dependent enhancement (Stickgold, 2005). The interactions between memory formation and sleep have been investigated in rodents, where it has been shown that hippocampal neuron ensembles replay activity patterns that occurred during the awake experience (see Wilson & McNaughton, 1994, and multiple more recent efforts that have extended those discoveries and reported a wide variety of replay phenomena). Replay of neuronal activity patterns still remains to be demonstrated in the human

hippocampus. Additionally, the relative easiness with which behavior can be examined in humans may pave the ways to a systematic investigation of the relationship between MTL activity during sleep and learning.

Epilepsy

The need to understand the mystery of the human brain is in itself one of the ultimate challenges of science. Yet, this need is largely driven by the goal of providing therapies for the variety of devastating neurological diseases including epilepsy, stroke, movement disorders such as Parkinson's disease, and Alzheimer's disease and other dementias. This goal is present and clear especially in the clinical situations that provide unique data, such as in single neuron recordings in humans, which are performed only in settings of neurological disorders.

In spite of significant progress in our understanding of the origins and mechanisms that give rise to epilepsy, 20–40% of patients with epilepsy remain medically refractory (Engel et al., 2012). Advances in drug development might help reduce, or hopefully one day even eliminate, the number of patients with pharmacologically intractable seizures. In the meantime, two ongoing efforts might make significant strides to reduce or eliminate seizures.

One of these involves using invasive devices to detect or even predict seizures in real time and then using electrical or pharmaceutical stimulation methods to stop the seizures (Sun et al., 2008; Morrell and the RNS System in Epilepsy Study Group, 2011). While there has been significant progress in seizure detection algorithms, seizure prediction remains a daunting problem (Mormann et al., 2007). Recently, encouraging evidence from a prospective long-term trial has been reported (Cook et al., 2013).

The higher spatial resolution of single neuron recordings could potentially provide key missing circuit-level constraints to improve seizure prediction. We expect to see major advances in this field in the next several years.

In refractory cases where invasive intervention is an option (Engel et al., 2012), we expect that the higher resolution of microelectrode recordings (single unit or localized field potentials) may help guide and improve the surgical approaches (Schevon et al., 2008; Stead et al., 2010; Truccolo et al., 2011; Alarcon et al., 2012; Bower et al., 2012; Schevon et al., 2012; Valdez et al., 2012; Mormann & Jefferys, 2013). While these and similar studies demonstrate correlations between single cell properties and later focal seizure onset location, whether these methods are useful to predict the seizure onset zone has not been tested so far in a rigorous blinded study (see discussions in chapter 18). It may be possible in the future to further delimit the boundaries of the epileptogenic areas, thus leading the way to smaller, more focal surgical resections in treatment of pharmacologically resistant epilepsy. This may help reduce potential cognitive deficits that could be associated with larger resections.

Single neuron studies could potentially be useful not only in delineating where seizures originate but also in determining whether nonepileptogenic tissue is sufficiently functional. This is of high clinical interest, as the functionality of resected areas needs to be supported by the tissue

that remains. Most often this is assessed with limited spatial resolution using the Wada test (also called the intracarotid sodium amobarbital procedure), but alternatives or additional supporting tests are an active research topic and include functional neuroimaging mapping techniques. As an example for a different possible approach using neuronal recordings, novelty-sensitive neurons within the MTL exhibit differential sensitivity in putative epileptogenic versus nonepileptogenic areas (see chapter 7 and figure 11 in Rutishauser et al., 2008). This suggests that the extent of novelty sensitivity of MTL neurons might serve as an indicator for which part of the MTL is functional, a hypothesis that remains to be tested directly but that is supported by lesion studies (Knight, 1996).

Additionally, the combination of single neuron recordings and field potential recordings may shed light on the elusive nature of interictal discharges and high-frequency oscillations (Engel & da Silva, 2012; Jacobs et al., 2012; see also chapter 18). Understanding the nature and origin of these discharges might help localize epileptic activity as well as its propagation in the brain.

Brain tissue that results from removal of the putative epileptic focus can be utilized to perform in vitro experiments that permit intracellular or molecular work not possible in vivo (Williamson et al., 1993; Kohling et al., 1999; Kohling & Avoli, 2006). Such tissue can exhibit epileptic phenomena such as interictal sharp waves (see chapter 18). This tissue offers the unique opportunity to use standard laboratory techniques such as the whole-cell patch clamp to record from human neurons. This can be used to test anti-epileptic drugs as well as to test hypothesis on abnormal network organization. While rarely utilized at present, we expect significance advances in the future that will utilize such tissue.

Deep Brain Stimulation

Deep brain stimulation (DBS) has become part of the tool arsenal to treat a variety of motor disorders (see chapters 17 and 18). The placement of DBS electrodes for therapeutic ends has also been a source of single and multiunit activity data, as recordings of these units has often been an integral part of the identification of optimal therapeutic targets (Engel et al., 2005). Additionally, a number of intriguing and potentially transformative applications of DBS are currently under intense investigation. One such application involves attempts to enhance learning and memory formation in Alzheimer's patients via bilateral fornix DBS (Laxton et al., 2010; Laxton and Lozano, 2012). Other work has shown that DBS applied to entorhinal cortex at the time of learning can enhance spatial memory (Suthana et al., 2012). Other interesting applications of DBS involve the treatment of epilepsy as well as several psychiatric disorders such as obsessive– compulsive disorder and major depression (Anderson & Lenz, 2009), also part of an ongoing clinical trial.

Treatment of movement disorders—principally Parkinson's disease (PD), dystonia, and essential tremor—with implantation of chronic DBS electrodes is often highly effective and is performed routinely (Hariz, 2012; Lozano & Lipsman, 2013). However, the mechanism by which stimulation acts is poorly understood, and it is unclear why in some cases DBS works almost

instantaneously (such as subthalamic nucleus stimulation for PD) whereas in others the latency to effectiveness can be very long (such as globus pallidus interna stimulation for dystonia). Also, there is considerable debate about the appropriate target structures as well as whether the primary treatment effect is due to stimulation or inhibition of cell bodies or fibers of passage. While effective, DBS treatment can also result in severe side effects. Better understanding of the mechanism and targeting of DBS is expected to significantly enhance treatment effectiveness while at the same time minimizing side effects.

Target structures are frequently identified by intraoperative microelectrode recordings (see chapters 15 and 16). These recordings can be performed anywhere along the track to the target structure, thus providing access to a number of areas within the basal ganglia, striatum, and thalamus. This technique has already revealed numerous features of both normal and abnormal function (see chapters 12, 15, and 16). Microelectrode recordings, potentially combined with subdural intracranial field potential recordings during DBS placement (Crowell et al., 2012), offer an exciting opportunity to record from brain areas impacted in movement disorders. Different movement disorders have fundamentally different underlying disease mechanisms (i.e., PD vs. dystonia), meaning that the different patient populations can serve as controls for each other. This enables investigation of disease-specific effects otherwise not possible (see de Hemptinne et al., 2013, for an example of this approach). Additionally, it should be possible to combine neuronal recordings in closed-loop systems, with real-time data analyses and electrical stimulation in different locations, timings, and frequencies dictated by actual physiological variables.

Motor Prostheses

The last decade has seen astounding progress toward developing neural prosthetic devices that can interact with the human brain to restore motor capabilities to quadriplegic patients (e.g., Carmena et al., 2003; Musallam et al., 2004; Schwartz, 2004; Hochberg et al., 2012, reviewed in chapter 17). The synergistic work across investigations in monkeys and humans can lead to important progress in these devices. Despite the advances, these devices remain under investigational inquiry and have not yet reached clinical use. Widespread adoption is held back due to factors such as limited repertoire of motor capabilities achieved, limited electrode lifetimes, clunky wires and connections, neurosurgical risk and complexity, and so forth.

Researchers are working diligently to address each of these limitations. It is conceivable that a combination of more electrodes, a better understanding of the encoding of motor signals, and exploitation of the remarkable plasticity of brain circuits may lead to an increased repertoire of motor abilities. Increasing the longevity of implanted devices with more robust electrode designs or with algorithms that use LFPs in addition to spiking activity could minimize and eventually obviate the need for periodic invasive surgery to replace the electrodes. The development of wireless and subcutaneous fiber optic technologies to transmit the signals to end effectors could minimize infection risk and further provide the patient with an outward appearance

indistinguishable from that of a healthy control subject. Emerging neurotechnologies might dramatically reduce the cost and complexity of surgically placing the electrodes.

While considerable work has been done toward upper limb prostheses, we might also see clinical trials of lower limb prostheses in the form of brain-controlled exoskeleton devices. Such devices may come to incorporate sensory feedback to improve the capabilities of the exoskeleton. Thus, hitherto fantastical science-fiction creations such as Luke Skywalker's prosthetic arm in *Star Wars* may become reality for the benefit of amputees or paralyzed patients.

Neurotechnology

New technologies often open doors to examine phenomena in a different way. The rapid pace of progress in the development of neurotechnologies to examine brain function can have tremendous impact in how we invasively investigate the human brain. We foresee progress on several fronts here, including the following:

1. *Further development of techniques to process and decode data in real time* This was briefly discussed in chapter 6. Real-time experiments may permit a level of interaction with patients not possible with offline studies. Real-time data processing may transform experiments as well as provide new solutions to clinical challenges as noted above (in the "Epilepsy," "Deep Brain Stimulation," and "Motor Prostheses" sections).
2. *Wireless transmission* Wireless transmission of signals may help alleviate cumbersome cables, provide more mobility to the patients, and reduce the risk of infections.
3. *Better signal isolation* Single unit isolation is always challenging, and overcoming noise is a perennial theme in human neurophysiological recordings.
4. *Novel types of electrodes* While it is often difficult to evaluate new electrodes in human recordings, several new types of technologies are being examined in animal models, and the knowledge from animal neurophysiology may be translated to human neurophysiology.
5. *Microdialysis combined with neurophysiology* Intriguing and promising initial observations were made upon combining microdialysis and electrode recordings (Fried et al., 1999; Blouin et al., 2013). While these efforts are not devoid of challenges, they may open the opportunity for direct interrogation of neuronal activity in the context of the surrounding chemical milieu and eventually, in the future, local application of different drugs.
6. *Brain–machine interfaces* Prosthetic devices for motor applications have been at the center of investigational efforts as these have a very clear and attainable use in neurological patients inflicted with paralysis such as in spinal cord injury, amyotrophic lateral sclerosis, and traumatic injuries (see the "Motor Prostheses" section above). Yet, the ability to directly interface the brain with the environment may be utilized to enhance other brain functions in different patient populations. Speech neuroprosthetic devices may be developed based on deciphering the neural code governing speech. For example, single neuron studies in humans uncovered a neural code for vowels involving different coding scheme in medial frontal and superior temporal regions

(Tankus et al., 2012). Yet, this is only a first step, and more complex schemes may yet be discovered by direct recordings from the human brain. For example, a neural code for images of specific individuals was used by Cerf et al. (2010) to construct a four-neuron brain–machine interface (see chapter 11). Initial experiments have already shown that electrical stimulation with DBS is capable of enhancing human memory (Laxton et al., 2010; Suthana et al., 2012) in some situations. Going even further, others have proposed to replace entire brain structures such as the hippocampus with electronic chips (Berger et al., 2005). The intention is to replicate the function of a brain structure such that, for example, a hippocampus damaged by seizures can be replaced to reestablish normal function.

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