Human Intracranial Recordings and Cognitive Neuroscience

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Abstract

The ultimate goal of neuroscience research is to understand the operating mechanism of the human brain and to exploit this understanding to devise methods for repair when it malfunctions. A key feature of this operating mechanism is electrical activity of single brain cells and cell assemblies. For obvious ethical reasons, scientists rely mostly on animal research in the study of such signals. Research in humans is often limited to electrical signals that can be recorded at the scalp or to surrogates of electrical activity, namely magnetic source imaging and measures of regional blood flow and metabolism. Invasive brain recordings performed in patients during various clinical procedures provide a unique opportunity to record high-resolution signals in vivo from the human brain—data that are otherwise unavailable. Of special value are the rare opportunities to record in awake humans the activity of single brain cells and small cellular assemblies. These recordings provide a unique view on aspects of human cognition that are impossible to study in animals, including language, imagery, episodic memory, volition, and even consciousness. In the current review we discuss the unique contribution of invasive recordings from patients to the field of cognitive neuroscience.

Contents

Electroencephalography (EEG): a noninvasive method for recording the brain's electrical activity by placing recording electrodes over the scalp. The measured signal corresponds to ionic current flow from large neural populations (mostly pyramidal cells)

Functional magnetic resonance imaging/blood oxygen level–dependent (fMRI/BOLD): the most commonly measured signal in functional MRI studies. The BOLD signal measures changes in blood oxygen content that are used as a proxy to estimate the underlying neural activity

INTRODUCTION

In the past, advances in the study of the human brain relied on a number of sources for scientific data. Seminal histological studies by Cajal, Golgi, Brodmann, Vogt, and others using animal brain tissue or human tissue obtained either postmortem or during surgery provided invaluable information about brain structure at the micro- and macroanatomical levels (De Carlos & Borrell 2007, Loukas et al. 2011). Brain function (as opposed to structure) was mainly inferred from clinical cases [such as the works of Wernicke (Thomson et al. 2008) and Broca (Dronkers et al. 2007)] relating damaged brain structures to observed behavioral deficits. Further insight was provided by noninvasive recordings of electric and magnetic signals from the human scalp, namely electroencephalography (EEG) since Berger's seminal discovery (Berger 1929), and later magnetoencephalography (MEG). A unique and important source of information regarding brain function was provided by neurosurgeons such as Penfield and others who recorded electrical activity or electrically stimulated the brains of neurosurgical patients during clinical procedures (Penfield 1950). Over the past few decades, technological advances have supplemented these tools with advanced neuroimaging methods that allow probing the structure and function of the living human brain in patients and healthy subjects in a noninvasive manner. These techniques have opened exciting new research fields that are now addressing the relationship between brain structure, function, and behavior.

Noninvasive tools can be largely classified into two categories on the basis of the type of information they provide—structural or functional. Structural tools such as computerized tomography (CT), magnetic resonance imaging (MRI), and diffusion tensor imaging (DTI) provide images that are static in time. The anatomical information can range from emphasizing, for example, gray matter, white matter, cerebrospinal fluid, blood vessels, or fiber tracks. On the other hand, functional tools such as EEG, MEG, positron emission tomography (PET), and functional MRI (fMRI) provide information about the temporal dynamics of various physiological measures. These dynamics are most relevant because they allow examining the relationship between physiological measures in specific brain regions while the subject is engaged in various tasks and cognitive states that change in time. However, given that the brain communicates and functions by electrical activity of individual neurons at millisecond resolution, all noninvasive techniques suffer from poor spatial and/or temporal resolution.

Certain clinical procedures involve invasive recording of electrophysiological measures in patient populations for clinical purposes. These procedures provide a unique opportunity to probe the human brain at high spatio-temporal resolution, which is otherwise unavailable. Some of the advantages these techniques provide include:

(*a*) Signal source. Invasive techniques allow direct recording of the electrical activity from populations of cells or even individual cells while techniques such as fMRI

or PET record surrogate signals (such as blood flow or metabolism rate), which are indirectly linked to the electrical activity of very large neural populations.

(*b*) Spatial resolution. Targeting and localization of implanted recording electrodes is within ~1–2 mm. Depending on the type of signal recorded (see below), electrodes can measure the spiking activity of individual neurons or the local field potentials from populations of neurons within a diameter of a few millimeters. For comparison, source localization of EEG or MEG signals provides an effective spatial resolution that is an order of magnitude lower (~1 cm).

(*c*) Temporal resolution. Invasive recordings have millisecond resolution (similar to EEG and MEG), which is compatible with the timescale of neural activity. For comparison, the fMRI signal measures slow hemodynamic fluctuations that are on the timescale of seconds.

(*d*) Signal-to-noise ratio (SNR). Invasive recordings have higher SNR compared with scalp EEG and MEG. Noninvasive methods are more susceptible to artifacts (due to eye blinks and movement), and the signal is weaker because it has to pass the cranium and scalp before reaching the recording electrodes. The higher SNR provided by direct invasive recordings allows examination of high-frequency bands that are unavailable from scalp recordings.

(*e*) Spatial distribution. In some invasive procedures (see below), recordings are performed from multiple brain regions simultaneously, providing relatively large coverage of the brain.

(*f*) Human cognition. By far, the major advantage of invasive recordings in humans over similar recordings in animals is the possibility to address questions that are unique to human cognition and behavior such as language, episodic memory, imagery, volition, and emotion. These aspects of human cognition clearly lack an experimental animal model and are unavailable at high spatio-temporal resolutions using noninvasive techniques.

Although these advantages are pertinent, it is important to note the following limitations of such recordings:

(*a*) Subject population. The most obvious limitation is the fact that these recordings are only conducted in patients with various pathologies and clear clinical justification for performing these procedures. Therefore, it can be argued that results from such recordings might not always generalize to brain function in healthy population. Nevertheless, as in the case of epileptic patients, recording sites typically include multiple brain regions and not only the region eventually found to be pathologic.

(*b*) Limited spatial distribution. In many cases sampling is directed to a few targets, and it is never targeted to whole brains.

(*c*) Study time. Study time for performing the recordings is limited and constrained by the clinical setup, therefore making long experiments impractical. Depending on the type of recording (acute or semichronic; see below), the duration of a typical experimental session can range between 15 and 40 minutes.

(*d*) Medication. The patients are usually under various medication regimens that might affect the functional properties of recorded tissue. This can be often controlled for by performing the recordings when the patients are tapered off medication or alternatively recording from many patients who are on different medication types and therefore diminishing the effect (if any) of specific medications.

(*e*) Homogeneity of subjects. Relative to studies on healthy volunteers, patient populations may be more heterogeneous and range in age, cognitive skills, and task performance levels. These factors add variability to the collected data.

Local field potentials (LFPs): extracellular voltage changes resulting from both dendritic currents and action potentials of populations of neurons. These signals are typically recorded invasively using thin (submillimeter) microwires

In the current article, we provide an overview of the various invasive recording techniques available in humans, the type of signals that can be measured, and the relevant clinical populations in which there is clinical opportunity to perform such recordings. We continue by highlighting unique contributions of such studies to various fields in cognitive neuroscience. We conclude by pointing out fields in cognitive neuroscience in which invasive techniques will undoubtedly prove useful in future research.

RECORDING TECHNIQUES AND SIGNAL TYPES

Invasive procedures allow recording of the extracellular electrical activity from the brain at two levels of resolution—either at the level of action potentials emitted by individual (or very few) cells (single or multi units) or at the level of local field potentials (LFPs), which are the electrical signals resulting from the activity of large populations of cells near the electrode tip. Whereas the action potentials reflect the local processing and output of the cells, the LFP signal most probably reflects both action potentials and synaptic activity localized to the dendrites, thus corresponding better with the input to the cells. Depending on the type of implant, recording sessions can be conducted in the operating room (acute), the hospital ward (semichronic; between several days and two weeks or longer), or in a chronic manner (see Brain-Machine Interface section). Acute recordings are performed during surgery and are therefore typically short (~15 minutes), whereas recordings from electrodes implanted semichronically can be longer (~30 minutes, across multiple sessions) because recordings are performed during the patient's stay at the ward.

Several types of electrodes are commonly used:

(*a*) Subdural strips/grids. These are one- or two-dimensional arrays (strips or grids, respectively) of platinum-iridium or steel electrodes with a diameter of 2–4 mm and spaced several mm apart, although more dense arrays have been recently developed (Viventi et al. 2010). These electrodes are typically implanted under the dura, over the exposed cortex, and allow recording of the field potentials from the underlying brain tissue. Implantation is usually semichronic, allowing recording over periods of several days/weeks (**Figure 1*A***, *top*).

(*b*) Depth electrodes. Unlike subdural electrodes, depth electrodes penetrate the brain parenchyma in order to target deep brain structures. These electrodes allow recording field potentials from contacts along the electrode shaft. Additionally, microwires can be inserted into the core of the shaft to allow recording of single/multi-unit activity from the tip of the electrode (Fried et al. 1999) or along the shaft (**Figure 1*B***, *top*). Another type of depth electrode is the hybrid depth electrode (HDE), which has high-impedance contacts for recording action potentials from single/multi units interspersed between low-impedance contacts for recording the electroencephalographic signal (Howard et al. 1996b). Using multiple, closely placed microwire tips (as in the case of stereotrodes or tetrodes) improves the yield and isolation of single from multi units (Gray et al. 1995). Depth electrodes can be used in acute or semichronic fashion depending on the procedure (see Clinical Opportunities section below).

(*c*) Intracortical electrodes. These are electrodes that penetrate the cortex by a few millimeters and allow recording unit activity and LFP from superficial regions. The Utah array is a matrix of 10 × 10 electrodes that allows simultaneous recording from up to 100 channels (Nordhausen et al. 1996) (**Figure 1*B***). A linear array multielectrode is a thumbtack-shaped array of 20–24 electrodes, separated by 75–200 μm, that are placed on the subdural cortical surface to allow recording of

LFPs and unit activity from distinct cortical layers (Ulbert et al. 2001). Another type of electrode is the neurotrophic electrode, which induces growth of cortical neurites into a recording chamber (Kennedy 1989).

(*d*) Microdialysis. These are probes that allow measuring neurochemical concentration from brain dialysate samples and can be inserted via the lumen of depth electrodes or along the shaft (Fried et al. 1999). These probes can be used in semichronic implantations for measuring levels of neurotransmitter release at different time points (During et al. 1994, During & Spencer 1993, Fried et al. 2001).

In addition to passive recording, some electrode types also allow electrical stimulation of the underlying tissue. This powerful combination makes it possible to stimulate one region while measuring activity in other regions and thus to examine the functional connectivity between them. In addition, stimulation allows the examination of causal links between neural activity in the stimulated region and overt behavior.

Clinical Opportunities

The opportunities to perform intracranial recordings of neural activity or to electrically stimulate neural tissue can be divided into two categories: acute situations during brain surgery (intraoperative) and chronic or semichronic conditions involving electrodes implanted in the human brain for diagnostic or therapeutic reasons.

Acute recordings and stimulation. Awake brain surgery for brain mapping was pioneered by Wilder Penfield, who kept his patients awake during surgery to be able to map functional properties of brain regions by using electrical stimulation. The lack of pain receptors in the brain allows stimulating brain tissue while patients are awake and examining correlated behavioral manifests (Penfield & Jasper 1954). This surgery was done mostly in patients with pharmacologically resistant epilepsy and was aimed at the safe resection of epileptogenic brain tissue when a focus for the seizures could be identified. Intraoperative stimulation and recording are carried out in modern neurosurgery in operations on a wide spectrum of patients, mainly those with epilepsy or brain tumors, where surgery is planned in brain regions critical for certain functions such as language, motor, or sensation (Ojemann 2010).

Another set of procedures, known as deep brain stimulation (DBS), is aimed at small functional regions within the brain. Electrodes are stereotactically inserted, and chronic stimulation is then used to ameliorate disabling symptoms in several neurological disorders. DBS for patients with Parkinson's disease and for patients with dystonia or essential tremor is now part of clinical practice in selected cases. DBS is also emerging as a potential therapy for patients with epilepsy and for patients with psychiatric disorders such as major depression and obsessive compulsive disorder. In the operating room, stimulation and extracellular recordings of neural activity are used to optimally identify the desired target for chronic stimulation. This provides the opportunity to examine cognitive and motor functions intraoperatively (Engel et al. 2005).

Acute recordings and stimulation in the operating room have the advantage of studying brain targets in the living brain under direct vision or stereotactic control, with the ability to move the electrodes while obtaining physiological data. However, clinical time constraints and the pressured setting of surgery limit the behavioral paradigms that can be employed.

Chronic or semichronic recordings. In certain neurosurgical conditions, electrodes are inserted inside the cranium for longer periods of time. In DBS procedures, electrode leads that are used for chronic stimulation are sometimes externalized before the pulse generator is inserted. Therefore, for a limited period of time,

Deep brain stimulation (DBS): involves chronic electrical stimulation of specific brain targets for therapeutic purpose, such as in treatment of Parkinson's disease or dystonia. This is typically achieved by a chronically implanted electrode and a pulse generator

usually several days, these externalized leads can be used for recording intracranial EEG (iEEG).

By far, the most common opportunities in contemporary neurosurgery to record neuronal signals from inside the human brain outside the operating room are in patients with intractable epilepsy who are evaluated for potential curative surgery. About 1% of the population suffers from recurrent epileptic seizures. Although in most cases medication helps control these seizures, in about one-third of the cases the seizures are resistant to pharmacological intervention, and surgical resection of the seizure focus may be the only clinical resort. In a small subset of these patients, noninvasive methods are not sufficient to identify a seizure focus. These patients then require placement of intracranial electrodes in order to identify a seizure focus for potential subsequent surgical removal. These electrodes may be subdural arrays of multiple contacts placed on the surface of the brain or depth electrodes placed at suspected targets inside the brain parenchyma. After electrode implantation, the patients are monitored around the clock for the occurrence of spontaneous seizures. Patients remain in the monitoring ward for a period of one to two weeks until sufficient clinical data for localizing the seizure focus are obtained. During this time the patients very often can participate in research studies. The research is done at no added risk to the patients, as the electrodes are already there for clinical reasons. Although in acute recordings electrode position can be adjusted, once the patient is out of the operating room, the electrode position during chronic recordings is fixed and cannot be adjusted to accommodate signal quality.

An obvious limitation in conducting neurophysiological research of cognitive functions in epilepsy patients is that recordings are carried out in brains that have abnormal electrical activity. However, it should be pointed out that recordings are performed in multiple suspected brain regions, and often merely a subset of these are eventually found to be involved in epileptogenic activity. Additionally, recordings are carried out during long periods when no seizures occur. Findings in epileptogenic regions can often be compared with findings in regions that are not involved. Finally, results from studies in these patients should always be interpreted in view of existing knowledge from animal neurophysiology and noninvasive neurophysiology in humans obtained by other methods. In the history of neuroscience, studies in epilepsy patients have provided important windows into normal brain mechanisms, as evidenced by seminal discoveries such as the motor homunculus in humans (Penfield & Boldrey 1937) and the distribution of speech and language areas in human cortex (Ojemann et al. 1989, Penfield & Roberts 1959).

It is expected that the opportunities to record signals from within the human brain will evolve in the near future to include novel developments in DBS and in the emerging field of brain-machine interfaces (BMIs). DBS is emerging as a potential therapy for neuropsychiatric disorders such as major depression and obsessive-compulsive disorders and cognitive enhancement in conditions of cognitive disorders and memory impairment. BMIs may use intracranial signals to modify human motor and cognitive abilities. Therefore, the study of signals recorded from the brain parenchyma relevant to human cognitive function may undergo substantial evolution in the coming years. We now describe various fields of cognitive neuroscience in which invasive clinical recordings have already provided valuable data.

Brain-machine interface (BMI): a communication channel between neural tissue and an external hardware device. BMIs include recording devices that use the recorded neural signal to control an external hardware device (e.g., a computer mouse) or stimulating devices (such as cochlear implant, or DBS) that send electric signals to the brain

COGNITIVE FUNCTIONS STUDIED BY INTRACRANIAL ELECTRODES

Perception

Throughout the brain, neurons are organized in an orderly fashion along various functional dimensions. A salient organization principle found in auditory cortex of experimental animals is tonotopy. Cells in auditory cortex form an anatomical gradient of sensitivity according to sound frequency. Consistent with animal studies, a tonotopic organization has been

demonstrated in humans with high frequencies represented in caudal medial Heschl's gyrus and lower frequencies in anterolateral regions (Howard et al. 1996a). Interestingly, the width of the tuning curves (i.e., the range of tone frequencies a single neuron is sensitive to) was found to be much narrower in humans than is expected based on recordings in most mammals (Bitterman et al. 2008). In visual cortex, iEEG studies demonstrate that receptive field size and response latencies increase from early regions (V1) to more anterior regions (V3/V4). Lateral regions (corresponding to middle temporal/middle superior temporal areas in monkey) have larger receptive fields, although response latencies are similar to those of V1 (Yoshor et al. 2007a).

In ventral visual cortex, a recurring theme is that of categorization. Neighboring cells within a small patch of cortex respond selectively to stimuli with similar attributes. Faces are an important stimulus category, and many studies using various techniques have shown that specific regions of the fusiform gyrus and inferior temporal gyrus respond preferentially to the visual presentation of faces. Invasive EEG studies have demonstrated that the negative component of the evoked response (N200) has higher amplitude during the presentation of human faces compared with many other stimulus categories (such as scrambled images, objects, and animals) (Allison et al. 1999). This selectivity is also invariant to changes in face representation such as color versus black and white, photo image versus line drawing, and size (McCarthy et al. 1999) (see also Seeck et al. 2001). Electrical stimulation of these regions corroborates these results by demonstrating temporary inability to name familiar faces or by evoking face-related hallucinations (Allison et al. 1994, Puce et al. 1999). Although the amplitude of the N200 component measured in iEEG studies is insensitive to degree of attention, noninvasive studies have shown that attention modulates the fMRI signal in face-related regions (for a similar discrepancy in V1, see Yoshor et al. 2007b). A recent iEEG study reconciles this apparent discrepancy in face-selective regions by demonstrating that although the N200 component is indeed invariant to the level of attention, gamma band LFP power modulations (30–100 Hz) are increased when attending a face (Engell & McCarthy 2010). Indeed, the fMRI BOLD signal in human sensory regions has been shown to correspond with modulations in the gamma band LFP power (Mukamel et al. 2005, Nir et al. 2007, Privman et al. 2007). These results demonstrate that different components of the electrophysiological signal show differential sensitivity to task aspects that are not always available to current imaging techniques.

Another stimulus category, letter strings, has also been shown to selectively engage specific regions in the fusiform gyrus (regions distinct from the face-selective regions described above). In one iEEG study, the early positive component of the evoked response (P200) in the posterior fusiform responded equally strongly to word and nonword letter strings, whereas the later positive component (P400) in the anterior fusiform responded preferentially to words (Nobre et al. 1994), suggesting additional processing perhaps through feedback mechanisms from other regions. Another region, in left ventral occipitotemporal cortex, has been suggested by imaging studies to be selective to written words [the visual word form area (VWFA)]. A recent case report in one patient has demonstrated that the evoked iEEG response in this region is indeed larger for words and that subsequent resection of this region resulted in a reading deficit at the behavioral level accompanied by lack of functional selectivity for words in the fMRI signal. These results provide both correlation and causal evidence linking activity in this region with the detection of written words (Gaillard et al. 2006).

Functional selectivity to specific categories (e.g., faces, tools, houses) has also been demonstrated in other studies measuring evoked responses (Privman et al. 2007) and gamma band power modulations in the LFP signal (30–70 Hz) (Fisch et al. 2009). Another category of visual stimuli that has received attention lately is body parts. Pourtois and colleagues compared

N200 or P400: modulations in the ERP signal contain negative and positive peaks at specific time points. N200 and P400 refer to negative (N200) or positive (P400) peaks in the ERP signal 200 or 400 ms poststimulus onset, respectively

Gamma band: the high-frequency range of oscillations in the LFP or EEG signal. The exact definition of this frequency range varies among studies, but it typically refers to frequencies higher than 30 Hz and lower than 130 Hz

Medial temporal lobe (MTL): specific anatomical structures in the MTL include the amygdala, hippocampus, parahippocampal gyrus, and entorhinal cortex

the responses evoked by presentation of pictures of human body parts with those evoked by presentation of faces, tools, and mammals. They report a focal region in right lateral occipital cortex demonstrating larger evoked responses to pictures of body parts compared with other stimulus categories. The location of this region is compatible with the extrastriate body area (EBA) described in noninvasive fMRI studies (Pourtois et al. 2007).

The iEEG studies described above demonstrate that distinct regions of cortex respond in a selective manner to various stimulus categories. This grouping into categories is complemented by a lack of sensitivity to low-level features (stimulus size, color, etc.). Such results could have two alternative underlying sources: (*a*) distinct but neighboring neural populations that are sensitive to different aspects of the stimulus, but due to low spatial resolution of recording techniques, they give rise to an invariant average population signal or (*b*) truly invariant cells that are anatomically grouped.

Single-cell recordings of spiking activity (as opposed to the iEEG signal which stems from the pre- and postsynaptic activity of large populations of cells) allow examining this issue at a much finer scale. Indeed, category selectivity has been demonstrated at the spiking level of individual neurons. In the medial temporal lobe (MTL), 14% of cells have been shown to respond preferentially to stimuli belonging to a particular category (faces, natural scenes, houses, famous people, or animals) (Kreiman et al. 2000a). The results in MTL suggest that category selectivity in ventral and lateral occipitotemporal cortex demonstrated at the population level by evoked responses might also hold true at the single-cell level. However, a direct comparison of selectivity between spiking activity and LFP in MTL shows nonoverlapping anatomical distribution of category representation between the two signals (Kraskov et al. 2007). Therefore, category selectivity at the single-cell level in regions outside MTL remains to be demonstrated.

Although visual category represents one level of abstraction, a different type of abstraction for specific images within a category has been demonstrated at the single-cell level. Individual cells—particularly in hippocampus and entorhinal cortex—have been shown to respond to particular images (~1–3 out of a total of ~100 different images presented to the patient), with neighboring cells responding to different stimuli. The selective response of these cells was invariant across stimulus representations such that a cell responding to an image of the Sydney Opera House responded also to many other images of the Sydney Opera House regardless of low-level features such as angle or lighting and did not respond to images of other buildings. Similarly, a cell responding to the picture of a particular famous actress responded regardless of different clothing or hairstyle and did not respond to pictures of other famous actresses (Quiroga et al. 2005). The same cells also responded in an invariant manner across modalities (i.e., for spoken words and text strings representing the same concept) (Quian Quiroga et al. 2009). Thus these neurons respond to a common concept, regardless of representation type (**Figure 2**).

Within different MTL regions, there seems to be a hierarchy. Neurons in parahippocampal gyrus respond earliest (~270 ms), in a less selective manner (i.e., respond to more stimuli), and in a similar fashion to repeated stimuli, whereas neurons in entorhinal cortex, hippocampus, and amygdala respond later (~400 ms), more selectively, and with reduced firing rates to repeated stimuli (Mormann et al. 2008, Pedreira et al. 2009). Indeed, electrical stimulation of the parahippocampal gyrus (and also amygdala) is less probable to evoke response in hippocampal formation compared with stimulation in entorhinal cortex and presubiculum (Wilson et al. 1990), supporting a hierarchy in their connections.

Taken together, neural activity in ventral and lateral occipitotemporal regions is anatomically grouped by response preference to specific stimulus categories (such as faces, letter strings, and body parts). As the neural signal propagates from high-order visual areas in occipital and inferior temporal regions to

structures in the MTL, there seems to be a hierarchy of processing, with neurons in parahippocampal gyrus responding earlier and in a less selective manner compared with neurons in entorhinal cortex, hippocampus, and amygdala. Neurons in the hippocampus respond to highly abstract concepts and are insensitive to low-level representation features.

Sensory stimulation and conscious perception. A physical stimulus can elicit different percepts across individuals or even different percepts within the same individual across different time points (as in the case of binocular rivalry or bi-stable perception of ambiguous stimuli; Rees et al. 2002). In the lack of a one-to-one correspondence between conscious perception and external objective measures, the experimenter must rely on the subjective report of the subject. Although experimental animals can report their perception, this requires extensive training that can affect the underlying neural system. Furthermore, imagery, which is an internally generated percept, is virtually impossible to study in animals. In what follows, we discuss single-unit and LFP studies examining the correlation between neural activity and conscious perception of visual stimuli in humans.

Flash suppression is a phenomenon in which one stimulus is presented to one eye and is consciously perceived. After a short period, a different stimulus is presented to the other eye (while the first stimulus is still presented to the original eye). Behaviorally, perception switches to the new stimulus. In a study using flash suppression, Kreiman and colleagues (2002) demonstrated that ~70% of neurons in MTL structures (i.e., amygdala, hippocampus, entorhinal cortex, and parahippocampal gyrus) follow perceptual alterations rather than retinal input. In other words, a neuron that responded selectively to one of the two stimuli (assessed during a previous monocular stimulation session) will respond during the binocular period only if the preferred stimulus is the one being consciously perceived. If the same stimulus is presented binocularly but is not consciously perceived, the neuron does not respond (Kreiman et al. 2002). Similarly, in a backward masking paradigm, Quiroga and colleagues (2008) parametrically changed the duration of picture presentation (from 16 ms to 256 ms) followed by a scrambled image serving as a backward mask. Behaviorally (especially for the short presentation durations), picture recognition was variable across trials, and neural firing rates in MTL correlated with recognition behavior. In other words, when a stimulus is presented for 66 ms, a selective neuron responds only on trials in which the patient recognized the picture, whereas on physically identical trials in which the stimulus is not recognized, the same neuron did not fire (Quiroga et al. 2008) (**Figure 3**). A similar correlation between perception and neural firing has been demonstrated using a change detection task (Reddy et al. 2006). In addition to these studies, the correlation between perception and neural firing is further supported by the fact that neurons in MTL that respond during visual perception of a specific picture respond also when there is no physical stimulus and the patient simply imagines the same picture

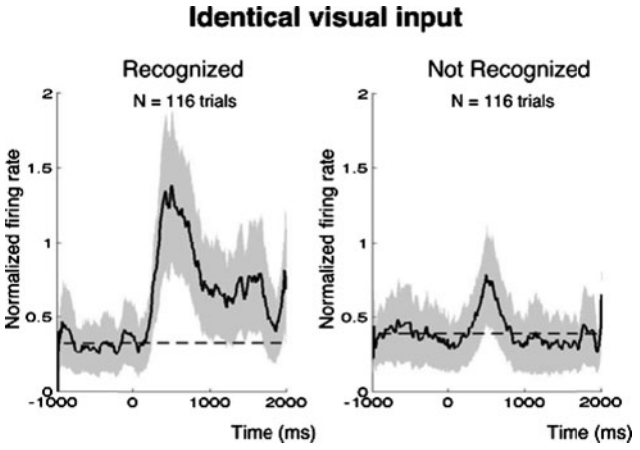

Figure 3

Neural activity and conscious perception. Stimulus perception can be manipulated by using short presentation durations and backward masking. In such conditions, perception varies from trial to trial even when identical stimulation parameters are used. The figure shows the average normalized firing rate of 29 MTL neurons during recognized and not-recognized trials (four trials in each condition). Note how the increase in neural activity corresponds with behavior. Reproduced from Quiroga et al. (2008) with permission.

Event-related potential (ERP): the EEG signal, locked to stimulus onset (or any other temporal event of interest), is averaged across many trials to produce the ERP. Only modulations that are locked to event onset will be evident in the ERP signal

(Kreiman et al. 2000b). Thus, firing patterns in MTL structures correspond to specific percepts whether externally or internally generated.

Although the studies described above focused on spiking activity, other studies have examined the correspondence between perception and LFP power modulations. Using a backward masking paradigm, Fisch and colleagues (2009) presented patients with pictures from various categories including manmade objects, faces, and houses. Pictures were presented for a brief period (16 ms) followed by a mask (250 ms), and perception was manipulated by changing the duration of an intervening blank screen between the two (16–200 ms). Perceived stimuli were characterized by enhanced gamma power (30–70 Hz) relative to nonperceived stimuli. This enhancement was pronounced in high-order visual areas and absent in retinotopic regions. Additionally, successful recognition was characterized by an increase in evoked response amplitude in high-order (and not low-order) visual areas in the temporal lobe (Fisch et al. 2009). In a similar vein, Gaillard and colleagues employed a masking paradigm using printed words. In the first 200 ms, masked and unmasked words elicit a similar evoked response and increase in the high gamma band (50–100 Hz) LFP power, mostly in posterior occipital and visual areas. After ~200 ms, the event-related potential (ERP) and gamma band signals decay for masked words while successful recognition is characterized by longer-lasting ERPs and sustained increase in the high gamma LFP power that propagates to occipital, parietal, and prefrontal regions (Gaillard et al. 2009).

Finally, electrical stimulation in low-level visual areas has been shown to elicit visual percepts. In V4 color-sensitive regions, electrical stimulation elicits color percepts that correspond with the color evoking the strongest LFP signal (Murphey et al. 2008). In more anterior regions (such as the fusiform face area), evoking face percepts corresponds better with long stimulations (5 seconds; Puce et al. 1999) compared with short stimulations (300 ms; Murphey et al. 2009).

Taken together, findings from invasive studies support the notion that the conscious perception of a stimulus is correlated with neural activity in MTL and the propagation of neural activity (measured by increased high gamma band LFP power) to high-order visual areas and parietal and frontal regions. The mechanisms underlying these neural correlates of consciousness are an important topic of further research.

Memory

In many respects, we are defined by our memories: from what we can do (procedural/skill memory), what we know (semantic memory), who we know (familiarity), and how we met (episodic memory). Deficits in any of these aspects of memory, such as in the case of dementia or amnesia, can have devastating consequences on our notion of self (Eichenbaum & Cohen 2001, Schacter 1996, Squire 2004, Tulving & Schacter 1990). Understanding the mechanisms that underlie successful memory formation—encoding, retention, and recall—has tremendous consequences on learning, cognition, and rehabilitation. Certain types of memories, such as fear conditioning or skill learning, are relatively amenable to manipulation in experimental animals. Other memory types, such as episodic, require self-report and are therefore extremely difficult to probe in animals. In the current section we review recent single-unit and iEEG studies addressing the neural mechanism of human memory. Because many of the epilepsy patients evaluated with invasive electrodes for identifying a focus amenable to surgical removal are implanted with electrodes in the temporal lobe, the opportunity to study declarative and episodic memory is especially pertinent, as it enables direct access to the critical MTL structures. MTL structures and particularly the hippocampus are chiefly responsible for our ability to transform percepts into lasting memories that are available for later conscious access.

The ability to distinguish between novel stimuli and stimuli that one has been exposed to in the past is an important aspect of memory, in

which the hippocampus and MTL structures play an important role (Corkin 2002, Squire et al. 2004). Recent studies suggest that both the hippocampus and amygdala contain subsets of neurons that modulate their firing rates to stimuli according to their degree of novelty (novelty versus familiarity detectors). Thus, in the case of familiarity detectors, the first encounter with a stimulus (encoding) does not elicit a significant neural response, whereas a second exposure (retrieval) elicits a robust and significant response. In the case of novelty detectors, a strong neural response during the first stimulus encounter is subsequently suppressed during repeated stimulus presentations. On the basis of the activity of a small pool of neurons in hippocampus and amygdala, the degree of novelty (whether the stimulus was previously seen or not) can be predicted with high accuracy, even if the behavioral response is erroneous. (Fried et al. 1997, 2002; Rutishauser et al. 2006). Interestingly, neuronal activity in entorhinal cortex during retrieval is better correlated with behavioral judgments (Cameron et al. 2001). Recordings from both lateral temporal lobe (superior and middle portions of the middle temporal gyrus) and more medial sections (inferior portion of middle temporal gyrus and collateral sulcus) suggest a functional/anatomical subdivision. Inferior/medial sites are more sensitive to specific stages of explicit memory (encoding, storage, or recall), and lateral regions are more active during recognition of previously seen stimuli (Ojemann et al. 2002).

Although these studies distinguished between "new" and "old" stimuli, a finer distinction is between familiar and recollected stimuli. In the case of familiar stimuli, subjects remember that the stimulus was previously seen, whereas for recollected stimuli they also remember the context (e.g., where on the screen the stimulus was presented) (Diana et al. 2007, Yonelinas et al. 2005). Cells in hippocampus and amygdala show a graded response during retrieval between new, familiar, and recollected stimuli. Thus, higher firing rate of a familiarity detector during retrieval corresponds with higher probability that the stimulus will be also recollected (Rutishauser et al. 2008). The involvement of the hippocampus in encoding is also supported by electrical stimulation studies showing that stimulation of the hippocampus during encoding to memory results in memory deficits (Coleshill et al. 2004, Lacruz et al. 2010). Further studies have shown that during encoding, firing rate as well as the degree of phase locking of spiking activity of hippocampal/amygdala neurons to the theta-band (3–7 Hz) LFP is predictive of subsequent memory recall (Cameron et al. 2001, Rutishauser et al. 2010). For stimuli that will be remembered in the future, spiking activity tends to occur at a specific phase of the theta-band LFP, whereas spiking activity during presentation of stimuli that are later forgotten are less phase locked. (Rutishauser et al. 2010). Phase locking of hippocampal spiking activity to the delta LFP band (1–4 Hz) (Jacobs et al. 2007) and stimulus-related LFP phase resetting (4–20 Hz) (Mormann et al. 2005) have been shown during virtual navigation and word memory paradigms.

As animals cannot readily declare their recollections, recall is a particularly difficult memory function to study in nonhuman primates and other animals. In a different set of studies, it has been found that the same neural network that is active during stimulus encoding is reactivated during successful retrieval (for review, see Danker & Anderson 2010). When presented with various audiovisual clips, individual neurons in hippocampus and entorhinal cortex increase firing rate to certain clips but not to others. When the subject is later asked to describe the various videoclips that were presented (in the absence of any sensory input), the same neuron that responded during encoding increased its firing rate ~1 second prior to the onset of verbal recall of the same specific clip (Gelbard-Sagiv et al. 2008). Indeed electrical stimulation of amygdala, hippocampus, and parahippocampal gyrus has been shown to evoke a sensation of déjà vu or déjà vécu (Gloor 1990, Vignal et al. 2007). In addition, the temporal correlations of spiking activity in hippocampal cells during stimulus presentation (how much the firing rate

at time t is predictive of the firing rate at time $t+1$) increase each time an audiovisual stimulus is repeatedly shown. The degree of this temporal correlation is also predictive of subjects' future recall performance, suggesting a mechanism for binding successive events across time (Paz et al. 2010).

The picture emerging from intracranial studies of the ventral pathways in humans is that of visual stimuli eliciting neural signals that propagate through visual areas in occipitotemporal lobes to MTL structures. Along this pathway, the neural representation becomes more and more selective to specific categories or exemplars within a category and invariant to different representations of the same stimulus. Thus, at the level of hippocampus and entorhinal cortex, the top of the visual hierarchy in the ventral stream, the cells exhibit both increased specificity in that they respond to a particular concept, be it a person or a place, yet at the same time they exhibit the highest degree of invariance and abstraction, ignoring low-level features. In MTL, stimulus presentation evokes a phase resetting in the low-frequency bands (1–8 Hz) accompanied by increased firing rates of specific neurons in a selective manner. Increased firing rates in MTL regions correlate with conscious stimulus perception. Successful encoding to memory is associated with spiking activity phase locked to the theta (3–7 Hz) band LFP oscillations. During retrieval, the same selective neural networks are engaged (Gelbard-Sagiv et al. 2008). Thus, the hippocampus and entorhinal cortex seem to be important nodes in transforming sensory input into abstract concepts that can be consciously recollected.

Spatial navigation. An important area of memory research involves the model of spatial navigation in rodents. "Place cells" are a special class of cells originally described in the rodent hippocampus. These cells increase their firing rates every time the animal is in a particular location in the environment, thus forming one node in a "virtual" map of spatial locations (O'Keefe & Dostrovsky 1971). Using a computer-simulated virtual navigation task, Ekstrom and colleagues demonstrated that cells in the human hippocampus increase their firing rate when the subject is in a particular place within the virtual environment (place cells). These cells are sensitive to position in space regardless of viewing perspective (i.e., if the subject is facing north or south). On the other hand, cells in parahippocampal gyrus were sensitive to viewing perspective (Ekstrom et al. 2003). In a subsequent study, it has been found that cells, mostly in entorhinal cortex, encode both position in space and direction of motion. In other words, some cells increase firing rates while traversing a specific location in space in a clockwise direction but not when traversing the same location in a counterclockwise direction (Jacobs et al. 2010). Another important class of cells described in the rodent entorhinal cortex is "grid cells." These cells fire at repeated spatial locations that are equally separated in distance and form triangular grid-like patterns across the environment (Hafting et al. 2005). Such cells in humans have not yet been directly identified by intracranial recordings, although supportive evidence has been provided by fMRI study (Doeller et al. 2010).

Place cells in the rodent hippocampus constitute high-level abstractions of the spatial environment, with specific cells representing a particular location in space and not another (selectivity), regardless of head position (invariance). In humans, the same principle guidelines characterize neural responses in the MTL. Place cells in human hippocampus are an obvious parallel. Interestingly, in humans, these principles hold not only for spatial locations but also for sensory (or imagined) percepts, raising the possibility that the selective and invariant responses demonstrated in human MTL are an evolutionary expansion of the place cells described in animal physiology and represent a special class of cells, "concept cells" (Fried et al. 1997, Quian Quiroga et al. 2008). Finally, during free recall, the same neurons in human MTL that were active during encoding are reactivated (Gelbard-Sagiv et al. 2008). Animal studies suggest a similar reactivation of traversed paths in rodent place cells during

sleep (Wilson & McNaughton 1994), providing another parallel between animal and human physiology.

Emotion

Emotion, pain, disgust, and reward are other functional dimensions that have been explored invasively in humans. In the amygdala and hippocampus, cells have been shown to respond selectively to specific emotional expressions and the conjunction of specific facial expressions and gender during recognition (Fried et al. 1997). Additionally, induced high-gamma-power increases in the amygdala have been shown to be selective to aversive versus neutral or pleasant visual stimuli (Oya et al. 2002) and fearful versus neutral/happy faces (Sato et al. 2010). The ERP signal is also larger for fearful faces versus faces displaying happiness, disgust, or neutral emotion (Krolak-Salmon et al. 2004). In the case of subliminal priming by briefly presented text words, the evoked response in the amygdala displays significant differences ~800 ms after stimulus onset to threatening versus neutral words despite the fact that the subject's recognition is at chance (Naccache et al. 2005). Neural activity in amygdala also correlates (some neurons positively and some negatively) with level of monetary value assigned to items (Jenison et al. 2011). Taken together, these results suggest that the amygdala is sensitive to stimulus valence regardless of conscious awareness.

Another recent iEEG study reports that induced gamma band (50–150 Hz) power changes in the ventral temporal cortex, probably including regions of the amygdala, can be used to decode happy/fearful faces (Tsuchiya et al. 2008). At the neuronal level, cells in the right ventromedial prefrontal cortex have been shown to respond to aversive stimuli (pictures of aversive scenes or fearful versus happy faces) with short-latency (~120 ms) inhibition of spiking activity (Kawasaki et al. 2001).

Although the amygdala and prefrontal cortex respond to fear, evoked responses in the ventral anterior insula are stronger for faces expressing disgust (Krolak-Salmon et al. 2003). Furthermore, electrical stimulation of the posterior insula elicits painful and nonpainful somaesthetic sensations (Ostrowsky et al. 2002). In frontal cortex, neurons in the anterior cingulate cortex (ACC) have been shown to respond to noxious (thermal or mechanical) pain, although electrical stimulation did not elicit these feelings (Hutchison et al. 1999). Neurons in the ACC have also been shown to respond to words with high emotional valence (Davis et al. 2005) and to attention-demanding tasks (Davis et al. 2000). Finally, cells in this region increased firing rate during a motor response following perceived reduced reward, suggesting that this region links reward-related information with a change in motor plan (Williams et al. 2004).

Language

Substantial insight into the distribution of speech and language functions in human cortex was advanced by Penfield and colleague (Penfield & Roberts 1959) and later by Ojemann and colleagues (Ojemann et al. 1989). The latter authors point to substantial variability in language organization in the dominant hemisphere. The "language sites" in the dominant hemisphere, where electrical stimulation alters language and speech function, were also found to have characteristic changes in the event-related potentials to language stimuli (Fried et al. 1981). Ojemann and colleagues, as well as Bechtereva and colleagues, have recorded single-neuron activity acutely from awake epilepsy patients undergoing language mapping during surgery (Bechtereva et al. 1991, Ojemann et al. 1988, Ojemann & Schoenfield-McNeill 1999). Neural activity in anterior temporal lobe (mostly superior temporal gyrus) has been shown to be associated with listening to certain combinations of consonants, word length, or syllable structure (Creutzfeld et al. 1989a), whereas in the middle temporal gyrus, more neurons respond to overt speaking than to listening alone (Creutzfeld et al. 1989b). Despite hemispheric dominance to language (assessed by intracarotid sodium amobarbital

Induced response: in many cases, neural activity is not time-locked to the external event but nonetheless is triggered by it. In such cases, the LFP signal will exhibit increased power at certain frequency bands evident in the spectrogram. These power changes are sometimes, but not always, accompanied by an evoked response

procedure or electrical stimulation), laterality in neural activity during language tasks was not found (although neurons in the dominant hemisphere may respond earlier).

More recently, sequential processing of lexical, grammatical, and phonological information has been demonstrated using iEEG recorded from Broca's area (Sahin et al. 2009). In this study, subjects had to either read words out loud or inflect a base word (single/plural or past/present) according to a sentence shown earlier. In some cases (null inflection), the base word was appropriate and did not require further conversion, whereas in other cases (overt inflection), a conversion was needed. Responses in Broca's area were triphasic. The initial response ~200 ms after word onset was sensitive to word frequency, with stronger responses to infrequent words. The subsequent response ~320 ms after word onset was sensitive to task. In the reading condition, the evoked response was weaker, and in the inflection condition, it was stronger (regardless of inflection level null or overt). The final response ~450 ms after word onset was sensitive to the degree of inflection, with the strongest response to overt inflection and a weaker response to null inflection (Sahin et al. 2009). These results demonstrate that different linguistic aspects are processed at different time windows within Broca's area. The anatomical location of responsive electrodes corresponded to fMRI activations from the same patients during the same task (and activation sites obtained from healthy subjects), demonstrating spatial congruency between techniques. However, the temporal resolution of the fMRI does not allow differentiating between the fast temporal components described above.

Self-vocalization has been also examined using iEEG. During speech production, the auditory-evoked response in lateral superior temporal gyrus is suppressed, and induced responses in the high gamma band are restricted to vocalization onset. During playback of the same speech (i.e., in lack of speech production), the evoked response and power modulation in the high gamma band are more pronounced. These results suggest that during speech production, premotor regions send efference copies that modulate neural activity in auditory cortex (Greenlee et al. 2011). For single-unit activity during self-vocalization, see Creutzfeld et al. (1989b).

Listening to speech elicits auditory-evoked potentials and event-related increases in gamma (>70 Hz) band power in postero-medial Heschl's gyrus. When speech is time compressed, spiking activity and LFP power modulations follow stimulus envelope even at high compression rates where speech is unintelligible. Evoked responses, on the other hand, failed to follow stimulus envelope at high compression rates (Mukamel et al. 2010b, Nourski et al. 2009). Taken together, these results suggest that the ability of spiking activity and high gamma LFP power modulations to follow stimulus envelope is not a limiting factor in speech comprehension.

Motor Cortex and Volition

A salient attribute of primary motor and somatosensory cortex is that of an organized representation of body parts (somatotopic organization). In the precentral gyrus, electrical stimulation of neighboring regions elicits movement in adjacent body parts, forming a map in which the entire body is represented, with the feet in the medial and dorsal regions and hand and mouth in the ventral and lateral regions. In humans, such somatotopic maps in primary motor and somatosensory cortex (on the postcentral gyrus) were first described by Penfield & Boldrey (1937), who used electrical stimulation during operations on neurosurgical patients.

In the supplementary motor area (SMA), electrical stimulation evokes movement mostly on the contralateral side, with a progression from feet movement during stimulation in caudal regions and head and neck movement during stimulation of more rostral sites (Fried et al. 1991; see also Lim et al. 1994). Similarly, iEEG recordings have shown a high gamma band power increase in sensorimotor cortex during contralateral movement that is in agreement

with a somatotopic organization (Crone et al. 1998a). Somatotopic organization has also been reported when examining alpha (8–13 Hz) and beta (15–25 Hz) band power decreases; however, these are more widespread and bilateral (Crone et al. 1998b). Regions exhibiting power increases in the gamma band and decreases in the low-frequency bands during hand and tongue movement have been also shown to correspond with evoked movement during electrical stimulation (Miller et al. 2007). At the level of single cells, a somatotopic organization has been demonstrated in the subthalamic nucleus (STN) of patients with Parkinson's disease (Abosch et al. 2002, Rodriguez-Oroz et al. 2001, Romanelli et al. 2004) and in sensory thalamus recording in patients with pain following spinal cord transection (Lenz et al. 1994).

Although the existence of a rough mapping of body parts in different motor regions has been demonstrated many times, it is not clear whether the organizing principle behind this is indeed anatomical proximity of body parts or rather action categories, with actions involving similar effectors (i.e., grasping or pulling with the hand) grouped in similar anatomic locations. Further studies are needed to clarify this point.

In addition to somatotopic organization, spiking activity of SMA neurons has been shown to correspond with movement speed and direction. Firing rates show an inverse relationship with speed, with lower firing rates preceding higher speed movements (Tankus et al. 2009). Neurons in SMA (and also in pre-SMA) have been shown to increase firing rate also during a preparatory delay period preceding action execution. Interestingly, SMA neurons also responded during imagery of motor movement (Amador & Fried 2004). At the population level, power increases in high-frequency LFP bands (76–100 Hz) and power decreases in low-frequency bands (8–32 Hz) have been shown during hand and tongue movement. During motor imagery, power changes in the same electrodes (but with lower amplitude) are observed. Electrical stimulation of these electrodes evoked movement in the corresponding body part, suggesting a shared representation for movement whether physically performed or imagined (Miller et al. 2010). This is similar to the overlapping representation of perceived and imagined visual stimuli in MTL structures described previously.

Although electrical stimulation of the SMA can evoke movement, in some cases it can also elicit an "urge" to move, as reported by the patients, even in lack of any overt movement (Fried et al. 1991). Indeed, a recent report demonstrates that spiking activity in SMA proper and pre-SMA not only precedes motor action but can also predict the time point at which the subject reports first feeling the urge to perform the motor act (Fried et al. 2011). Another study reports that stimulation of inferior parietal cortex evokes the feeling of an urge to move and that increasing stimulation intensity even produces the illusion that the movement was performed (even in the absence of any overt movement or EMG signal). In contrast, stimulation of the premotor regions (lateral BA 6 excluding the SMA) produced overt movement that was denied having any volitional aspect by the patients (Desmurget et al. 2009). Stimulation of the anterior part of the SMA (most probably pre-SMA) has been shown to evoke laughter, which is perceived by subjects as voluntary and is accompanied by them providing a context-dependent cognitive explanation for it (Fried et al. 1998). A similar phenomenon has been reported with fusiform and parahippocampal gyrus stimulation (Arroyo et al. 1993). Further invasive recordings will be invaluable in elucidating these fascinating phenomena.

Linking action and perception. Recent findings in macaque monkeys have demonstrated that cortical regions predominantly engaged in motor output, such as the ventral premotor cortex and rostral part of parietal cortex, also respond in lack of overt movement but during perception of similar actions. The activity of such motor neurons "reflects" perceived actions performed by others; thus, they have been termed mirror neurons. In humans, single-cell

recordings demonstrate that a subset of neurons in SMA respond during action execution (facial gestures or hand grasps) and also during observation of these acts performed by others. Interestingly, such functional overlap between observation and execution of actions also has been shown in some MTL regions (parahippocampal gyrus, hippocampus, and entorhinal cortex), suggesting that not only motor cortex is sensitive to perceived actions performed by others, but sensory cortex is also sensitive to self-performed actions (Mukamel et al. 2010a). In the anterior cingulate, a similar overlap of neural firing rate during pain reception and observation of someone else receiving a painful stimulus has been shown (Hutchison et al. 1999). At the population level, iEEG studies show that motor and language regions that exhibit reduced alpha power (7.5–12.5 Hz) during finger tapping also show reduced alpha power during observation of finger tapping (Tremblay et al. 2004). Similar reduction in mu rhythm (12–20 Hz) is also seen in motor cortex for action sounds (finger clicks) (Lepage et al. 2010). In the insula, regions exhibiting enhanced ERPs during observation of disgusted facial expressions also elicit a feeling of disgust during electrical stimulation (Krolak-Salmon et al. 2003). Taken together, these studies suggest multiple overlapping neural representations for self and other, providing a link between perceived and executed actions that might facilitate communication across individuals and nonverbal learning.

INTRACRANIAL ELECTROPHYSIOLOGY AND FUNCTIONAL MRI

The use of fMRI as a neuroimaging tool has grown exponentially over the past two decades. This is mainly due to several advantages it offers over other available techniques. First, it is noninvasive and does not involve injecting radioactive tracers (as in PET). Furthermore, the discomfort to subjects during the scan is relatively minor (lying still, albeit in a confined, noisy space). Second, it allows recording signals from the entire brain (unlike EEG or MEG, which do not reach subcortical regions). Third, the spatial resolution is better than that of all other noninvasive techniques. Although these advantages are pertinent, the major drawback of the fMRI method is the indirect, and not fully understood, relationship of the measured signal with underlying neural activity (Logothetis 2008).

The BOLD fMRI signal measures changes in oxygen level that are used as a proxy to estimate underlying neural activity. The degree of coupling between this surrogate signal and different aspects of the electrophysiological signal that triggers it (namely spiking activity or local field potentials) has been a hot topic of research over the past decade. Due to the benefits of fMRI described above and its potential use as a noninvasive clinical tool, it has become increasingly important to resolve this issue of coupling between the fMRI signal and underlying electrophysiology. Invasive studies in humans provide a unique opportunity to compare the two signals in the living human brain.

Several studies have examined the degree of correspondence between the fMRI signal and electrophysiology in sensory, motor, and premotor cortex. Puce and colleagues (1995) have measured the fMRI signal while patients performed a motor task or during tactile stimulation of the hand. The sensory-motor regions of the same patients were also mapped electrophysiologically by cortical stimulation of motor cortex (to elicit hand/finger movement) and by recording evoked responses in somatosensory cortex during tactile stimulation of the hand. fMRI and electrophysiological mapping yielded anatomically congruent results demonstrating that fMRI can provide valid noninvasive localization of the hand representation of sensory and motor cortex (Puce et al. 1995). In another study, Brovelli and colleagues compared changes in gamma band LFP power in premotor cortex from one patient, with the fMRI signal from a group of healthy subjects performing similar tasks contrasting spatial attention with motor instruction/preparation. Gamma band

(60–200 Hz) power increases recorded from the patient colocalized with the fMRI activation sites, with preferential activation in the dorsal aspect of premotor cortex during the spatial attention aspect of the task and preferential activation in cingulate gyrus and SMA during the motor instruction/preparation aspect of the task (Brovelli et al. 2005).

In sensory cortex, Puce and colleagues (1997) have recorded evoked responses and fMRI activation patterns in two patients during presentation of face stimuli. The ERP N200 component and the fMRI activations were compatible and colocalized to the right fusiform gyrus (Puce et al. 1997). Compatibility between fMRI activation patterns and cortical function has also been demonstrated in the posterior temporal lobe. Schlosser and colleagues reported that electrical stimulation of cortical sites involved in language (as assessed by fMRI) produce language deficits (Schlosser et al. 1999). Other studies using a semantic versus visual discrimination task have also demonstrated spatial congruency between fMRI activations and gamma band (40–150 Hz) power increases in superior temporal gyrus and inferior frontal gyrus (Lachaux et al. 2007). Repetition effects, comparing activation to new versus old words, have also demonstrated fMRI signal colocalization with gamma band LFP power (70–190 Hz) in occipitotemporal, inferior parietal, and dorsolateral prefrontal cortex (McDonald et al. 2010). Similar colocalization was found in temporal lobe during a paired-word task (Ojemann et al. 2010).

In another study, Huettel and colleagues (2004) compared intracranially recorded ERPs from patients with the fMRI BOLD signal from healthy subjects during presentation of static checkerboards with variable duration (between 100 and 1,500 ms). In the peri-calcarine cortex, both the fMRI signal and LFP power in the gamma range (20–45 Hz) increased monotonically with stimulus duration. In the fusiform gyrus, on the other hand, the fMRI signal increased with stimulus duration whereas the LFP power did not (although this discrepancy might be due to the lower-frequency range examined in this study compared with others) (Huettel et al. 2004).

The correlation between electrophysiology and fMRI in visual cortex has also been demonstrated using dynamic stimuli. Privman and colleagues (2007) have shown that during presentation of an audiovisual movie segment, the gamma band (30–70 Hz) LFP power fluctuations along the hierarchy of visual areas correspond with the temporal dynamics of the fMRI signal of healthy subjects in the same regions. In auditory cortex, Mukamel and colleagues (2005) recorded spiking activity and local field potentials from patients and compared them with the fMRI signals recorded from healthy subjects exposed to the same audiovisual segment. The results demonstrate a strong correlation between spiking activity, gamma band (40–130 Hz) LFP power modulation, and BOLD fMRI signal in auditory cortex during natural audiovisual stimulation.

From the studies mentioned above, the emerging picture is that in sensory (visual, auditory, and somatosensory cortex) and motor regions there seems to be anatomical congruency between gamma band LFP power changes and the fMRI BOLD signal. In auditory cortex, there is also strong coupling between the temporal dynamics of spiking activity, gamma band LFP, and the temporal dynamics of the fMRI signal. In the hippocampus, on the other hand, this does not seem to be the case. One study measured the fMRI signal in patients during a virtual navigation task and subsequently measured electrophysiological signals (unit activity and LFPs) from the same patients in a different session. The results of this study demonstrate that the BOLD fMRI signal in the parahippocampal gyrus correlates with theta-band power changes (both increases and decreases), and in the hippocampus it correlates only to increases in theta-band power. In both regions, no correlation between neural firing rate and the fMRI signal was found (Ekstrom et al. 2009).

The differences in the coupling of fMRI signal and electrophysiological signals across different brain structures (sensory versus

medial temporal lobe) can be explained by different functional properties. Nir and colleagues (2007) have demonstrated that the coupling between the spiking activity and LFP/fMRI signal fluctuates in time and depends on the degree of spatial correlation among neighboring cells. When correlation between spiking activity of neighboring cells is high, the correlation between spiking activity and gamma band LFP is also high. When correlation between spiking activity of neighboring neurons is low, the correlation between spiking activity of individual neurons and gamma band LFP is also low. In both cases, the correlation between gamma band LFP and fMRI BOLD signal remained high (Nir et al. 2007). In other words, when large populations of neurons fire in a correlated pattern, a sample of the activity of few neurons is representative of the population activity and correlates with the local field and fMRI signals. When individual neurons fire in a decorrelated fashion, a sample of the activity of few neurons is not a good estimate of the population activity, and therefore correlation with the other two measures is low. Thus, the difference in the level of coupling between fMRI signal and electrophysiology in MTL structures compared with sensory regions could be due to differences in the functional (coding) properties of neurons in the two regions. Neighboring neurons in sensory regions tend to fire in a correlated fashion (e.g., columnar organization), whereas neurons in the hippocampus respond selectively to specific stimuli, with neighboring neurons responding to different stimuli, resulting in low spatial correlations and weak coupling to the fMRI signal.

Brain-Machine Interface

Recent advances in technology and science have set the stage for exploring the feasibility of restoring neurological functionality in disabled patients by creating a control interface between neural activity and computer devices. Such interfaces take one of two forms: either hardware devices providing input to the nervous system or the nervous system providing input to hardware devices. Deep-brain stimulators and cochlear implants are examples of devices that provide input to the nervous system by sending electrical impulses. Using neural activity as input for an external hardware device (such as a computer cursor, wheelchair, or robotic arm) is an example of communication in the other direction. The closure of the input-output loop creates a bidirectional interface in which the nervous system modifies the environment, which in turn modifies the nervous system, and so forth. The emerging field of brain-machine interface (BMI) provides not only potential for enhancement of function, but also precious insight into mechanisms of learning and neural plasticity, volition, and conscious control of neural activity.

The first step in designing a successful BMI is discerning the goal and degrees of freedom in the task that needs to be accomplished. For example, if the goal of the BMI is to move a computer cursor on a 2D screen, one needs two degrees of freedom (x and y planes) and to map neural signals into 2D space. On the other hand, controlling a multijoint robotic arm in 3D space involves many more degrees of freedom and requires mapping neural signals into a much higher dimensional space. The task the BMI needs to accomplish and the associated degrees of freedom determine the type of brain signals and spatio-temporal resolution that are required. The technical challenge is then to obtain these signals in a chronic and noncumbersome manner. For example, posthoc decoding of fMRI signals might be relevant for occasional communication with locked-in patients (Shoham et al. 2001) but is impractical for controlling a prosthetic limb on a daily basis. The next challenge is to develop smart algorithms that map the recorded raw signals into one specific state in the multidimensional space defined by the task. By itself, this mapping is not enough. It needs to be fast and efficient if the task requires real-time response. Finally, after mapping the raw signal to the relevant state, the specific goal-directed action associated with that state must be executed by hardware (e.g.,

move the computer cursor to the right). As if all these challenges were not enough, the ultimate bottleneck is whether or not a person can learn how to exert volition in order to control and switch between the relevant neural states. In other words, if neural state A is associated with action A′ and neural state B is associated with action B′– then the patient needs to be able to switch between neural states A and B at will.

Facing these challenges requires a collaborative effort spanning multiple fields including neuroscience, engineering, robotics, and computer science, to name a few. In the current section, we review developments in the field, focusing on single-unit studies for controlling hardware devices. For iEEG studies, see, for example, Felton et al. (2007), Kennedy et al. (2004), Leuthardt et al. (2004), Marquez-Chin et al. (2009), Reddy et al. (2009), and Wilson et al. (2006).

Several studies now have used spiking activity recorded from motor cortex to control an external device such as a computer cursor. In a locked-in patient suffering from amyotrophic lateral sclerosis (ALS), Kennedy and colleagues (Kennedy & Bakay 1998) recorded action potentials from right motor cortex using a neurotrophic electrode (Bartels et al. 2008, Kennedy 1989). The patient was asked to do "whatever mental activity" to increase or decrease neural activity of a group of recorded neurons while visual and aural feedback regarding firing rates was provided. Results demonstrate that the patient could switch between high/low firing rates when instructed to do so, thus proving volitional control of neural activity. In another patient (tetraplegic following a brainstem stroke), volitional increases in firing rates were demonstrated and further decoded into rightward cursor movement on the screen (1D). This controlled cursor movement allowed construction of sentences by moving the cursor to letters or icons on a virtual keyboard even 17 months after implant (Kennedy et al. 2000).

In another study, a tetraplegic patient was implanted with a 96 microelectrodes array in the hand area of primary motor cortex. The patient was asked to imagine different hand movements while spiking activity from small neuronal pools (3–57 cells) were recorded. These spiking patterns were successfully decoded to allow 2D control of a computer cursor on the screen (Hochberg et al. 2006). In addition to cursor movement, the same signal sources could be used to simulate a mouse click (Kim et al. 2007). In a subsequent study, two tetraplegic patients were implanted with electrodes in the arm representation of the left precentral gyrus. Spiking activity was used to control the 2D position of a computer cursor in a center-out task where the subject had to guide a computer cursor from a central position to peripheral positions upon instruction. Reliable decoding was achieved even ∼1 year after electrode implantation (Kim et al. 2008; see also Truccolo et al. 2008).

The studies described above demonstrate how neural activity can be used to simulate a computer mouse and control a cursor on a 2D screen. In another study, spiking activity recorded in left precentral gyrus was used to simulate vowel generation. The electrode was implanted in the speech motor region of a locked-in patient following a brainstem stroke, and signals were sent wirelessly to control a speech synthesizer. Speech dimensionality was reduced to three target vowel sounds (OO, A, and IY). Applying online decoding of spiking activity, hit rate reached 75% and movement time reached ∼4 sec after 25 training sessions over five months (Guenther et al. 2009).

In contrast to the chronic implantations in motor cortex described above, other studies performed intraoperative recordings in patients during a procedure for DBS implant. In one study, extracellular neural activity from ensembles of neurons in thalamic motor areas or the subthalamic nucleus was recorded. Patients were instructed to vary grip force on a squeeze ball, and feedback was provided visually by cursor position along the *x*-axis. Offline decoding of spiking activity demonstrated that activity from a small population of cells (3–55 cells) was sufficient to successfully predict the actual grip force that was used during recording (Patil et al.

2004). In another study, recordings from premotor regions (area 6) demonstrated that small neural ensembles contain information about the intention to move as well as the direction of movement (Ojakangas et al. 2006). The results of these intraoperative studies suggest that neural activity in subcortical as well as premotor regions contains parametric information that could be used in future BMIs. Whether patients can learn to exert volition on these signals in order to control an external device is not yet clear.

Motor imagery is known to evoke activity in corresponding cortical motor regions that are active during actual movement execution. Therefore, to date, most studies recording neural activity for the purpose of controlling an external device have focused on decoding signals from motor regions under the premise that it is more intuitive for patients to learn to modulate neural activity in those regions using imagery. In a recent study, Cerf and colleagues (2010) demonstrated volitional control of neural activity in medial temporal lobe. First, the visual selectivity of different MTL neurons was assessed (e.g., cell 1 in amygdala was found to respond to the visual presentation of picture A and not picture B, while cell 2 in entorhinal cortex was found to respond to picture B and not A). These response profiles were later used to successfully "guess" in real time the picture that the patient was thinking about. Interestingly, patients learned to modulate the activity of these neurons even if they were in different regions or hemispheres (Cerf et al. 2010). These results demonstrate that volitional control of neural states is not limited to motor cortex and that neural activity in MTL can also be used for future BMI purposes.

The studies described in this section demonstrate that we have the technology and scientific knowledge to record neural activity in a chronic manner and to decode this activity in real time as long as the dimensionality of the task is low (e.g., 2D movement of a cursor or selecting vowels in a three-vowel space). In motor cortex, it seems that even after years of paralysis, neurons retain a level of functional selectivity that can be used for this purpose. Patients can learn to control neural states in frontal and medial temporal regions. The big challenge remains: reading a high-dimensional neural code and transforming it into sophisticated computer code that will allow the control of assistive external devices with multiple degrees of freedom. In facing this challenge, chronic invasive recordings play an important role, providing insights into the basic mechanisms of learning, plasticity, and the conscious control of neural activity.

CONCLUDING REMARKS AND FUTURE DIRECTIONS

Recording signals from inside the human cranium is a small yet critical part of cognitive neuroscience research. It is positioned between invasive animal neurophysiology and noninvasive human studies using other techniques such as scalp EEG, MEG, fMRI, and clinical case studies. Although conducted in patients with neurological problems and only under strictly guided clinical procedures, these recordings provide a rare opportunity to probe electrical activity of single neurons and neuronal assemblies in the brain with high spatial and temporal resolutions, in conscious human subjects who can report their experience, declare their percepts and memory, and describe their wants and plans. Emerging diagnostic and therapeutic modalities, including implantation of dense microelectrode arrays, deep brain stimulation, and brain-computer interfaces present new opportunities for such recordings. Aside from the obvious benefit to patients, these modalities may provide insights into the mechanisms of neural plasticity, perception, learning and memory, language, imagery, emotion, motor planning, volition, and conscious control of neural activity. Neurosurgeons are in a unique position to probe the living human brain and elucidate the neural mechanisms of human cognition that cannot be directly accessed by animal neurophysiology or noninvasive human physiology (Abbott 2009, Crick et al. 2004).

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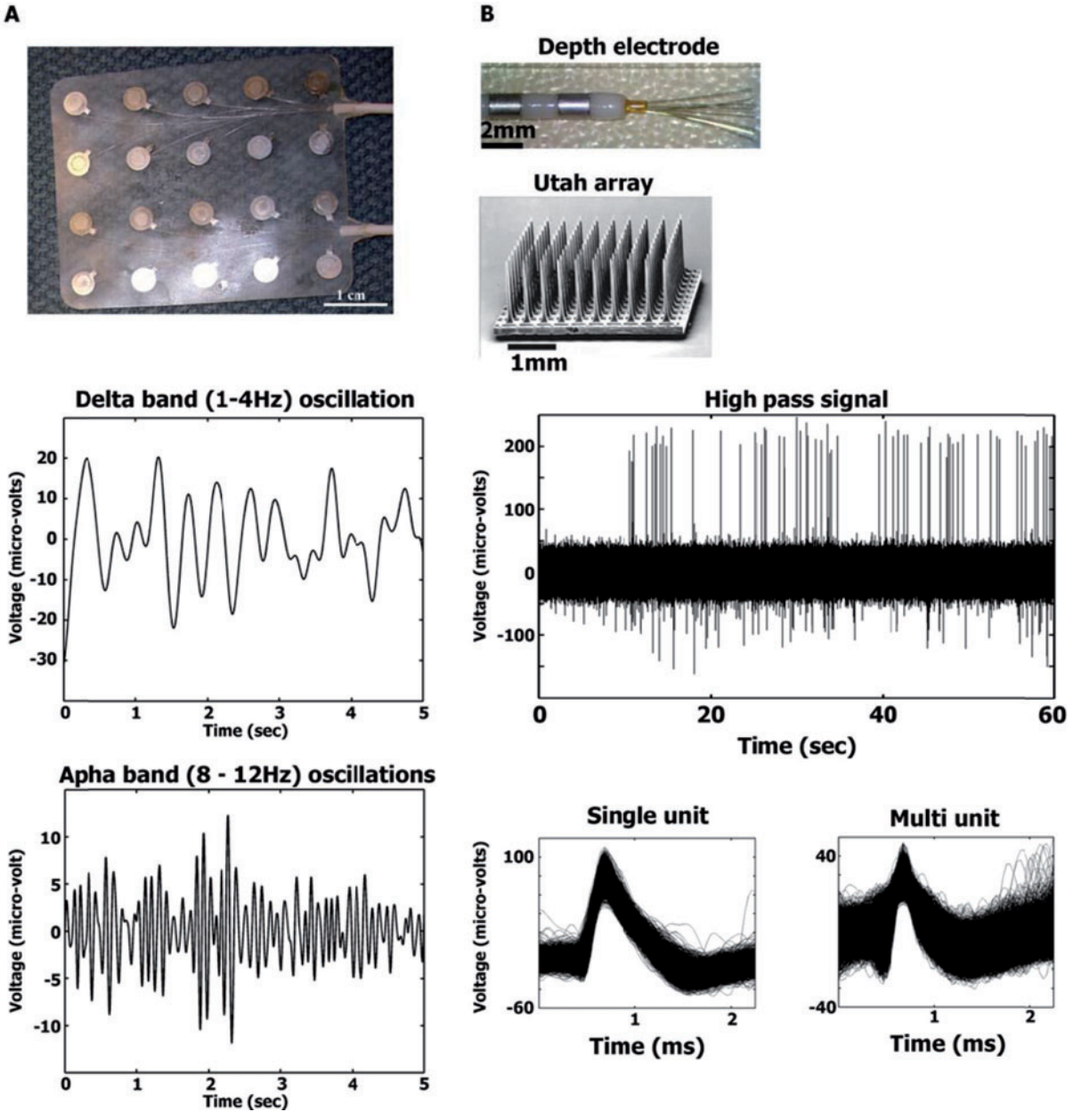

Figure 1

Electrode and signal types. (*A*) A 4 × 5 grid of intracranial electrodes for recording the iEEG signal (*top*). Filtering the recorded signal to different frequency bands (e.g., Delta, *middle panel*; Alpha, *bottom panel*) allows examining power changes across time and cognitive tasks. (*B*) Depth electrodes penetrate the brain parenchyma and allow targeting of deep brain structures. Contacts along the shaft allow recording of the iEEG signal while the microwires at the tip allow recording of high-frequency activity (*middle panel*) of single or very few neurons (*bottom panels*). The Utah array is a 10 × 10 matrix of electrodes that allow recording unit activity from superficial cortical regions (reproduced with permission from Hochberg et al. 2006).

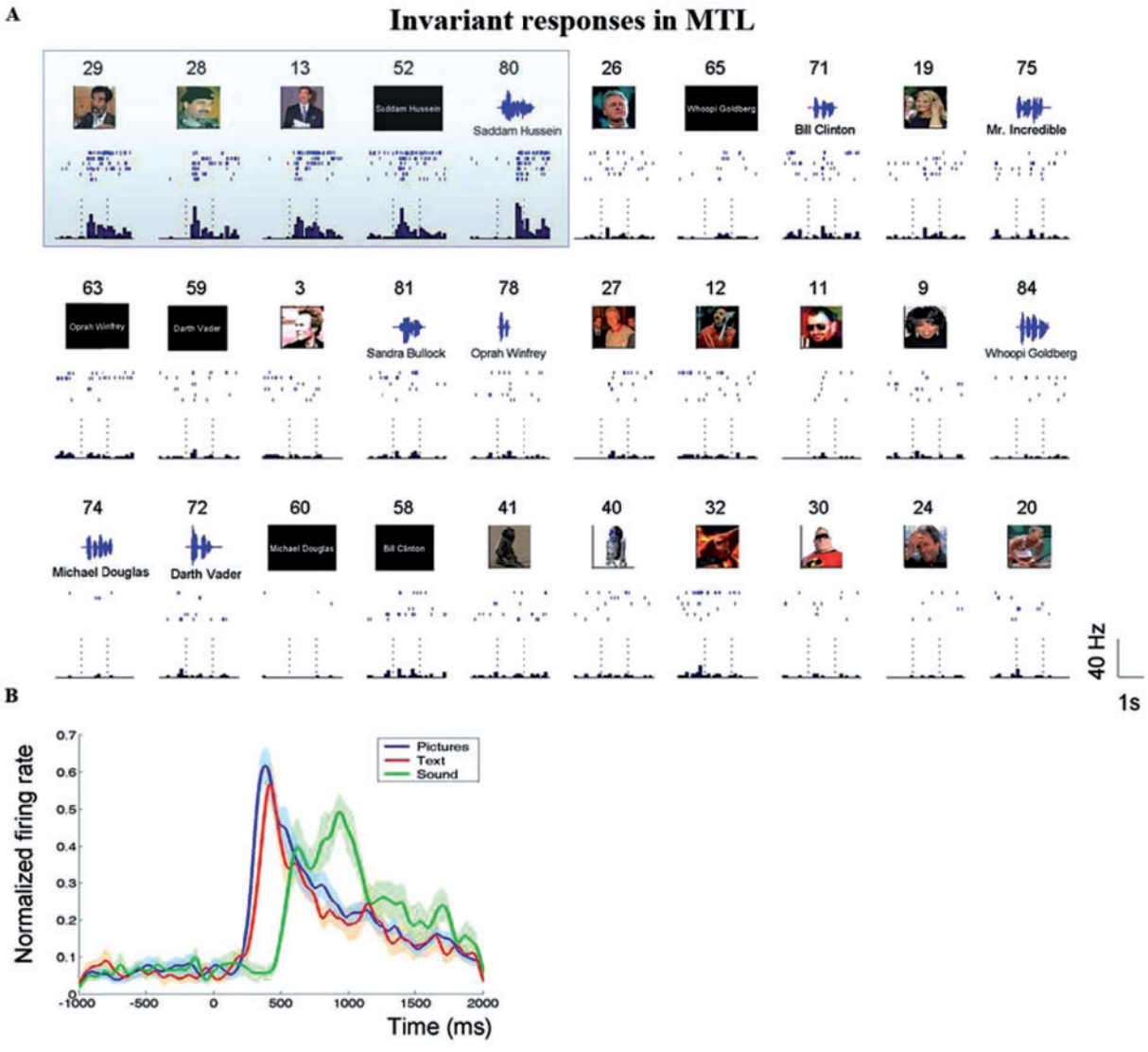

Figure 2

Selectivity and invariance. (*A*) Raster plots and peri-stimulus time histograms of a neuron in entorhinal cortex during visual presentation of pictures, text words, or auditory words. This cell responded selectively to the concept of Saddam Hussein and not to other stimuli. Regardless of low-level representation (different images of Saddam, the printed word of his name, or even the sound of his name), the neuron responded in an invariant manner. (*B*) Mean normalized firing rates of 17 medial temporal lobe neurons exhibiting invariance to low-level cues. Reproduced with permission from Quian Quiroga et al. (2009).

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