INVASIVE RECORDINGS FROM THE HUMAN BRAIN: CLINICAL INSIGHTS AND BEYOND

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Abstract | Although non-invasive methods such as functional magnetic resonance imaging, electroencephalograms and magnetoencephalograms provide most of the current data about the human brain, their resolution is insufficient to show physiological processes at the cellular level. Clinical approaches sometimes allow invasive recordings to be taken from the human brain, mainly in patients with epilepsy or with movement disorders, and such recordings can sample neural activity at spatial scales ranging from single cells to distributed cell assemblies. In addition to their clinical relevance, these recordings can provide unique insights into brain functions such as movement control, perception, memory, language and even consciousness.

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Despite the success of functional imaging in advancing our understanding of the human brain, our knowledge about physiological processes at the cellular level is largely inferential and based on comparative data from animal models. It is therefore fortunate that therapeutic approaches sometimes make it possible to carry out invasive recordings in the human brain, for example in patients with Parkinson's disease (PD) or with epilepsies that are resistant to pharmacological treatment. Invasive recordings can be indispensable for diagnosis of the disorder and for defining the appropriate treatment. Such measurements can involve the recording of LOCAL FIELD POTENTIALS (LFPs), which reflect the coherent activity of small CELL ASSEMBLIES, or the use of microelectrodes to measure single-cell activity. As these studies require well-defined clinical indications, they never yield data from normal brain circuits. Nonetheless, such data are valuable for understanding the pathophysiology of disorders and for linking animal models to the clinical situation. Beyond that, data from these studies can provide insights into the basic mechanisms of brain functions such as perception, movement control, memory formation, language processing and even conscious awareness.

This review provides an overview of current developments in the application of invasive recording techniques to humans and discusses approaches that link clinical applications with basic neurobiological and cognitive research. Invasive recordings have been developed primarily in two clinical contexts: in patients with movement disorders resulting from pathological changes in deep brain structures such as the basal ganglia or thalamus; and in patients with untractable epilepsies, where pathological neural activity needs to be localized before the epileptic foci can be surgically removed. In the latter group, recordings are made from the lateral surface of the cerebral hemisphere, focusing on the temporal, parietal and frontal lobes, or from depth electrodes that are, in most cases, advanced into the medial temporal lobe. We consider results that have been obtained in each of these brain regions, by single-unit recordings or by multisite unit or LFP recordings, and the insights that these results have produced. We also discuss possible future recording approaches and potential applications.

Invasive recordings in motor circuits

Direct neurophysiological recordings from human subcortical structures have become possible during stereotactic operations that are carried out for the

treatment of movement disorders such as PD, IDIOPATHIC DYSTONIA or ESSENTIAL TREMOR. The first attempts to record from the basal ganglia of patients with PD were made in the 1940s (see TIMELINE). Today, the subthalamic nucleus (STN) is the favoured target site in STEREOTACTIC NEUROSURGERY for PD[1]. The STN is routinely mapped using microelectrode techniques (BOX 1), and DEEP BRAIN STIMULATION (DBS) has largely replaced the earlier lesioning approaches[2]. DBS electrodes have also been implanted successfully into the internal segment of the globus pallidus (GPi) in patients with idiopathic dystonia[3], and into the ventral intermediate nucleus of the thalamus (Vim) in cases of severe essential tremor[4].

Clinical relevance of depth recordings. Microelectrodes are used in functional stereotactic neurosurgery to localize the target site for placement of lesions or a DBS electrode[5,6]. The upper and lower boundaries of the STN or GPi can be reliably determined by evaluation of firing rates and firing patterns, as these parameters show characteristic changes when the electrode enters or leaves these structures[5–7]. Patients are usually fully conscious during surgery to allow surgeons to test their motor functions and to monitor the effects of electrical stimulation. This makes it possible to study the relationship between single-cell activity in the target structure and movement of different body parts[8–12] or sensory stimulation[13]. The microphysiological study of these response properties and the resulting cell classifications have led to the definition of clinically useful topographies in the target structure on a scale that is much finer than is possible with neuroimaging techniques. For example, studies have revealed the somatotopic organization of the STN[8–10], confirming data that previously could only be obtained in animals.

Pathophysiological insights. Invasive recordings can also produce insights into pathophysiological mechanisms. None of the available animal models of PD, such as the MPTP (1-METHYL-4-PHENYL-1,2,3,6-TETRAHYDROPYRIDINE) PRIMATE MODEL, accurately reproduces all of the symptoms of the human disease (resting tremor, akinesia and muscular rigidity). Macaques that have been treated with MPTP develop severe akinesia and rigidity, but only rarely have classical resting tremor[14]. Moreover, most animal models do not reproduce the gradual dopaminergic degeneration that is characteristic of PD. For these reasons, it is crucial to test pathophysiological hypotheses directly in the human brain.

Tremor is a good example of a condition for which pathophysiological insights have been gained from invasive recordings in humans. Several studies in patients have focused on the cellular correlates of resting tremor. Cells that show synchronous rhythmical discharges associated with tremor have been found in various parts of the basal ganglia, including the external pallidum (GPe), GPi and STN[15–17], as well as in motor thalamic nuclei[11,13,17,18]. Such tremor-related cells are most abundant in the thalamus, particularly the parts that receive input from the cerebellum (such as the Vim), rather than from the basal ganglia output nuclei. Single-cell recordings from these thalamic regions have been used to classify cells as either responding to somatosensory stimulation or relating

LOCAL FIELD POTENTIAL
Extracellular voltage fluctuations reflecting the sum of events in the dendrites of a local neuronal population.

CELL ASSEMBLY
A spatially distributed set of cells that are activated in a coherent fashion and that are part of the same representation.

IDIOPATHIC DYSTONIA
A movement disorder that leads to involuntary sustained muscle contractions, causing distorted posturing of the foot, leg or arm.

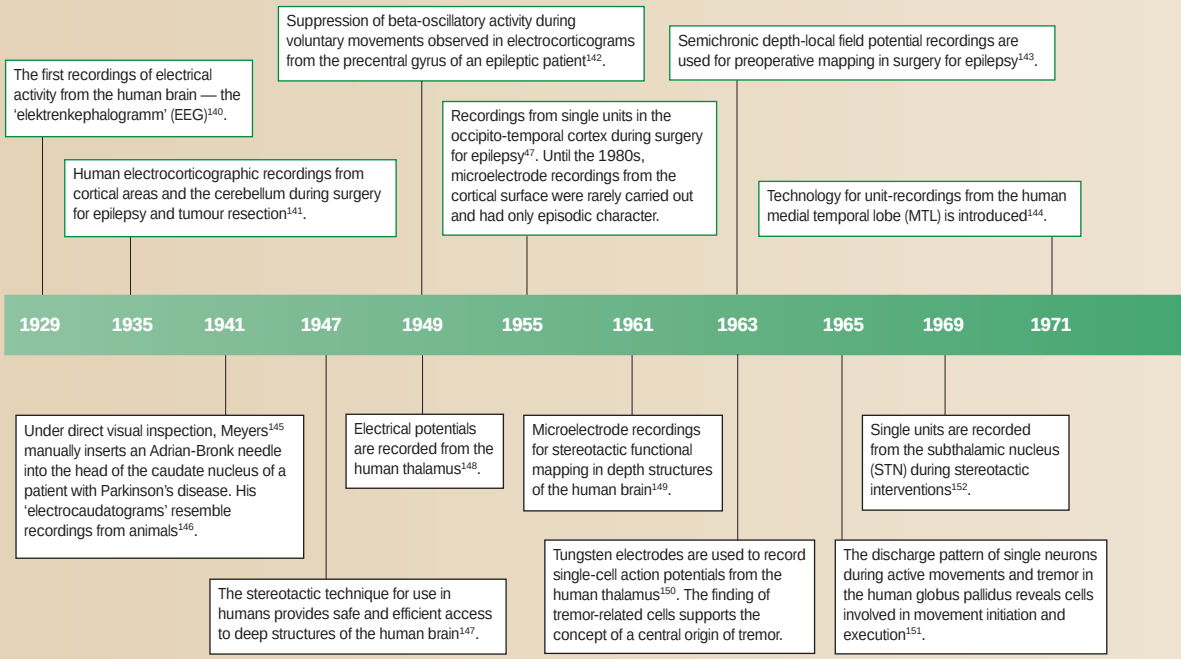
ESSENTIAL TREMOR
The most common neurological movement disorder. Symptoms include involuntary rhythmic movements of the limbs, head or neck.

STEREOTACTIC NEUROSURGERY
Microsurgical intervention in deep brain structures for lesion, biopsy or implantation that is based on careful planning using a three-dimensional coordinate system established with the help of neuroimaging.

DEEP BRAIN STIMULATION
A continuous application of short current pulses that is supposed to lead to functional blockade of basal ganglia nuclei.

MPTP PRIMATE MODEL
For the study of the pathophysiology of Parkinson's disease, monkeys are exposed to the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), causing degeneration of dopaminergic neurons in the substantia nigra.

Timeline | Milestones in the history of invasive recordings from the human brain



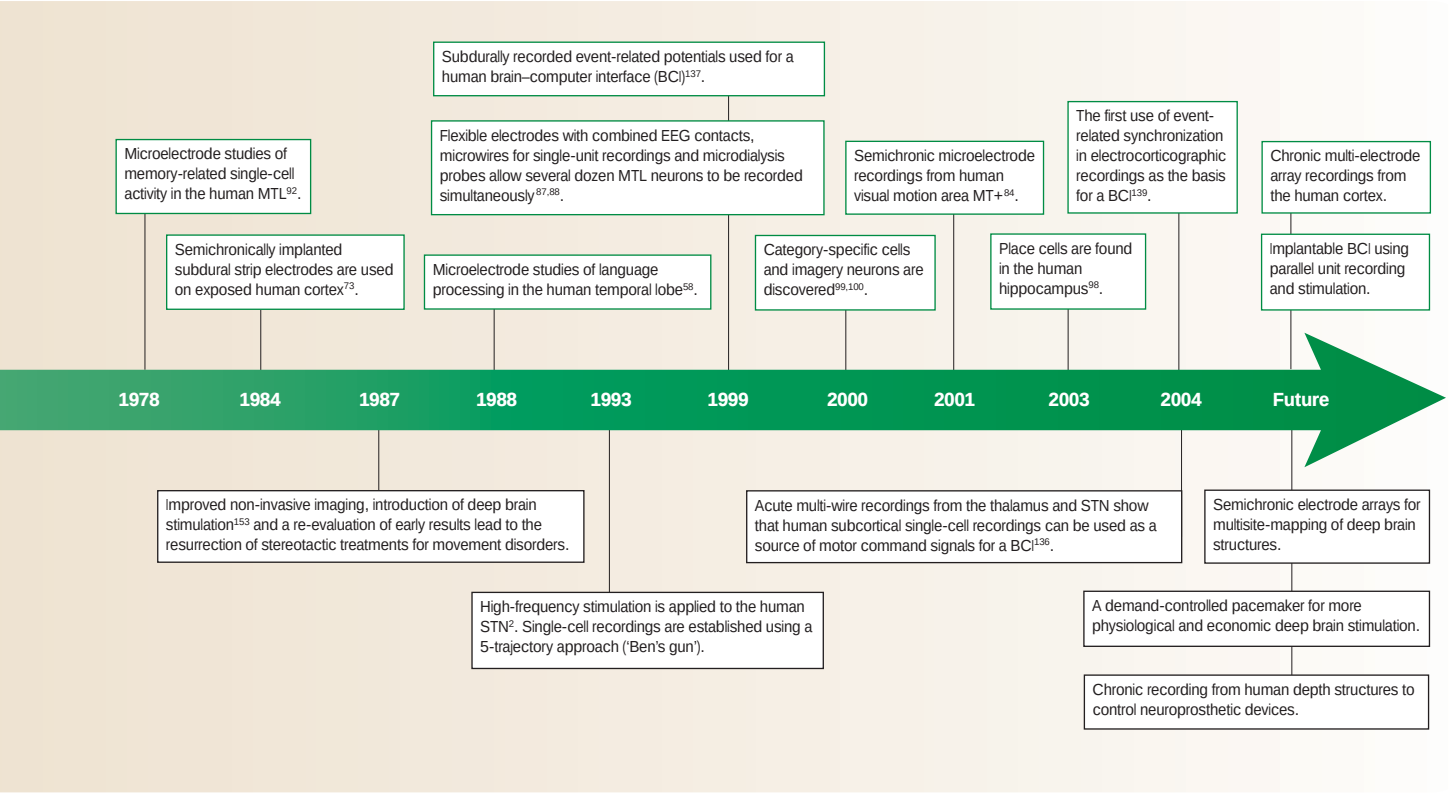
Green boxes indicate recordings in patients with epilepsy; black boxes indicate recordings in patients with movement disorders.

ELECTROMYOGRAM
Extracellular recording of muscle fibre activity.

to active movement of body parts. Interestingly, the activities of both cell types can be strongly correlated to the peripheral ELECTROMYOGRAPHIC (EMG) signal, but they differ in their phase relation to the tremor. Movement-related cells tend to lead in phase over the EMG, whereas sensory-driven neurons usually lag behind the EMG oscillation[13]. These data support a model in which PD tremor is driven by a central pacemaker that is modulated by sensory inputs[19]. So, thalamocortical cells could function as pacemakers that drive peripheral motor neurons through the motor cortex. The phase lag of sensory-driven cells, in turn, indicates that their activity is a result of sensory feedback generated in the periphery by the tremor. A closer analysis of the firing patterns of tremor-related cells[17,18] showed that the bursting behaviour is probably due to low-theshold Ca^{2+} conductances, which endow thalamic cells with filter properties that are involved in the generation of the 3–6-Hz tremor frequencies[19].

Towards a new pathophysiological model. Although most of the symptoms of PD result from the degeneration of nigrostriatal neurons, it is unclear whether they can be related to a common set of pathophysiological mechanisms. For instance, inactivation of the thalamic Vim nucleus consistently ameliorates tremor, but does not improve other parkinsonian features. By contrast, dopaminergic medication has stronger effects on bradykinesia and rigidity than on tremor[20]. Classical pathophysiological models of PD[21,22], which account for akinesia and bradykinesia by assuming enhanced firing rates in the GPi, are now considered limited in their explanatory power (for reviews, see REFS 14,23–25), and alternative accounts have been developed. One of the new models is inspired by data obtained in the MPTP primate model. In MPTP-treated monkeys, neurons in the GPe, GPi and striatum start to oscillate at tremor frequencies (3–8 Hz) and at frequencies in the beta band (15–30 Hz)[26,27]. These oscillatory firing patterns tend to be synchronized along the basal ganglia loop[27] and lead to abnormally patterned and synchronized firing in the motor cortex[28]. These findings lead to the suggestion that the normal dopaminergic system supports a segregation of functional subcircuits in the basal ganglia, and that a breakdown of this independent processing leads to abnormal temporal coupling and the emergence of the symptoms of PD[14,24].

This 'dynamic model' of basal ganglia function is supported by single-cell recordings in patients with PD, which have confirmed these findings of pathological synchrony. In patients with the tremolous form of PD, beta-band oscillations have been found in the ongoing activity of many cells in the STN, GPe and GPi (FIG. 1a), and these oscillations were prevented by dopamine agonists[16,29,30]. Recent multi-electrode recordings from the STN show that these oscillations can also occur in patients with the akinetic rigid variant of PD, who do not have a manifest resting tremor (C.K.E.M., A.K.E. and colleagues, unpublished observations; FIG. 1b). These oscillations are synchronized through almost the entire STN, indicating that there might be abnormally strong coupling in this frequency range.



Box 1 | Technology for invasive human recordings

Techniques for invasive recordings in human cortex or deep structures can be categorized into two groups depending on the timescale. 'Acute' single-unit recordings (over minutes or hours during surgery) typically use tungsten microelectrodes. For neocortical recording (FIG. 2), Ojemann and co-workers[56,58] developed a device with a ring-shaped footplate at the bottom of the microdrive that carries the recording electrode, which provides stable recordings from the exposed cortical surface by damping the pulsations of the tissue. A tetrode for use in humans was recently developed by Thomas Recording GmbH (Giessen, Germany). It consists of four platinum-tungsten fibres pulled in quartz glass with a distance of ~30 mm between the exposed tips. This tetrode provides sufficient information for optimal spike separation and has been used for recordings from the subthalamic nucleus and globus pallidus (J. Volkmann, H. J. Freund, V. Sturm, C.K.E.M. and A.K.E., unpublished observations). For acute basal ganglia recordings, a widely used device is 'Ben's gun'. Originally designed by A. H. Benabid[153], this multielectrode array consists of four outer electrodes separated by 2 mm from a central one, allowing a cylindrical volume of neural tissue to be mapped. With the five tracks advanced in parallel it is also possible to study interactions between neurons in different subregions of a structure (FIG. 1b). Multielectrode arrays have been developed for recording many neurons simultaneously. The Utah electrode array[120] is a silicon probe with 100 electrodes arranged in a 10 x 10 square grid separated from each other by 400 μm. It has not been tested in humans, but results from animal studies indicate that it might be useful in the human brain[120]. A linear 32-electrode array for mapping of deep structures has also been developed[154].

Devices for semichronic recordings typically remain in place for several days or weeks. Electrocorticographic recordings in patients with epilepsy often use subdural grids (FIG. 3). Typically, these grids consist of platinum–iridium or steel electrodes with a diameter of 3–4 mm embedded 1 cm apart in a silastic sheet[77,78]. The array can remain in place for several days. For depth recordings, electrodes are used that allow the acquisition of local field potential (LFP) signals from several contacts along the electrode[143]. Microwires can be inserted into the core of the macroelectrode[92], enabling unit activity and the depth LFP to be recorded simultaneously (FIG. 4). More recent designs include microdialysis probes, which can sample the extracellular fluid for neuroactive substances while recording from over 50 neurons[87,88]. For semichronic recordings of unit activity from the neocortex, Ulbert and colleagues[84,121] developed a linear array multielectrode with 20–24 platinum–iridium contacts separated by 75–200 mm. The thumbtack-shaped array is held in place by an anchoring silicon sheet that floats on the cortical surface.

LFP recordings from basal ganglia. The single-cell data are complemented by LFP recordings from the basal ganglia. The LFPs were recorded through DBS electrodes that had been implanted into the GPi or STN of patients with PD[31–34]. Simultaneously, the peripheral EMG was monitored and electroencephalogram (EEG) recordings were taken over sensorimotor cortical areas. This allowed the authors to investigate frequency changes or shifts in COHERENCE when the patient was under different states of medication or in different behavioural states. Consistent with the single-cell recordings, measurements without medication showed that, in the akinetic 'OFF' state, coherence between the basal ganglia and cortex is dominated by tremor frequencies and frequencies in the beta-band (below 30 Hz)[31] (FIG. 1c). Surprisingly, treatment with the dopamine precursor levodopa reduced low-frequency activity and resulted in a new coherence peak at 70 Hz in the gamma band (30–100 Hz)[31]. In a more formal task, high beta–gamma coherence was recorded during an isometric wrist movement in the pharmacological 'ON' state[32]. Importantly, electrical stimulation at those sites where beta-band coherence was highest with the EEG and the contralateral EMG yielded the best amelioration of Parkinsonian symptoms[32]. In another study[33], the functional significance of high-frequency activity was investigated by testing the modulation of coherence before and during voluntary movement. In the OFF state, beta-activity was suppressed during movement preparation and execution, whereas in the ON state, gamma-coherence was enhanced in relation to the movement[33]. LFP beta power in the STN is a good predictor for task performance. In a cued reaction-time task, beta-activity decreases before movement, and the onset latency of this decrease varies with the patient's reaction time[34].

Implications for basal ganglia function. These findings are compatible with a model in which interactions between the basal ganglia, thalamus and cortex in different frequency bands modulate basal ganglia functions in a task- and state-dependent way[35,36] (FIG. 1c). Slow oscillations at tremor frequencies or in the beta-band, resulting from dopamine depletion, seem to disrupt normal motor function. By contrast, gamma-band rhythms seem to be important for the organization of normal voluntary movement, as indicated by the emergence of these fast oscillations in the ON state, and by the prokinetic effects of DBS stimulation at these frequencies or higher harmonics[37]. It has been proposed that fast coherent rhythms are important for 'motor binding'[35,36]. Moreover, these synchronization processes could be related to the selection of movement patterns, acting through the thalamus to support cortico–cortical interactions in the gamma band[35]. This proposal is similar to the earlier idea[38] that temporal coherence of activity in cholinergic striatal interneurons could coordinate separate processing channels during learning. This 'dynamic model' of basal ganglia function might also lead to better understanding of the pathophysiology of dystonia and tremor, and there is strong evidence that both clinical conditions are related to abnormal temporal patterning in neural activity[39,40]. Interestingly, these conclusions, which were drawn from recordings in patients, agree with data on coherent oscillations in premotor and motor systems of animals[41–43], and with evidence that synchronized gamma-band oscillations are involved in binding and attentional selection in sensory systems (for reviews, see REFS 44–46). As discussed below, this unifying view is also suggested by invasive recordings from human sensorimotor cortices, which show enhanced gamma-band activity during sensorimotor tasks.

Invasive recordings from human neocortex

Surgical resections for medically refractory epilepsy are sometimes performed with the patient awake for part of the operation so that physiological findings can be used to plan the resection. In many patients, epileptic foci are found in the temporal lobe, with seizures originating from the hippocampus or the amygdalo-perihippocampal region. In such patients, microelectrode recordings (BOX 1) have been used to study the pathophysiological changes that occur in epilepsy[47–51]. In addition, such recording approaches have been used to address basic questions about neural coding and representation, particularly with respect to language-related capacities such as verbal memory, naming and reading[52].

COHERENCE
A normalized measure of neural interaction that shows high values when two signals share similar frequencies and adopt a constant phase relationship.

FOCAL EPILEPSY
A type of seizure with a localized site of onset.

ELECTROCORTICOGRAM
Direct recording of voltage fluctuations from the cortical surface.

CROSS-CORRELOGRAM
A histogram that describes the time relation between two signals, in which a centre peak indicates synchrony and side peaks reflect oscillations.

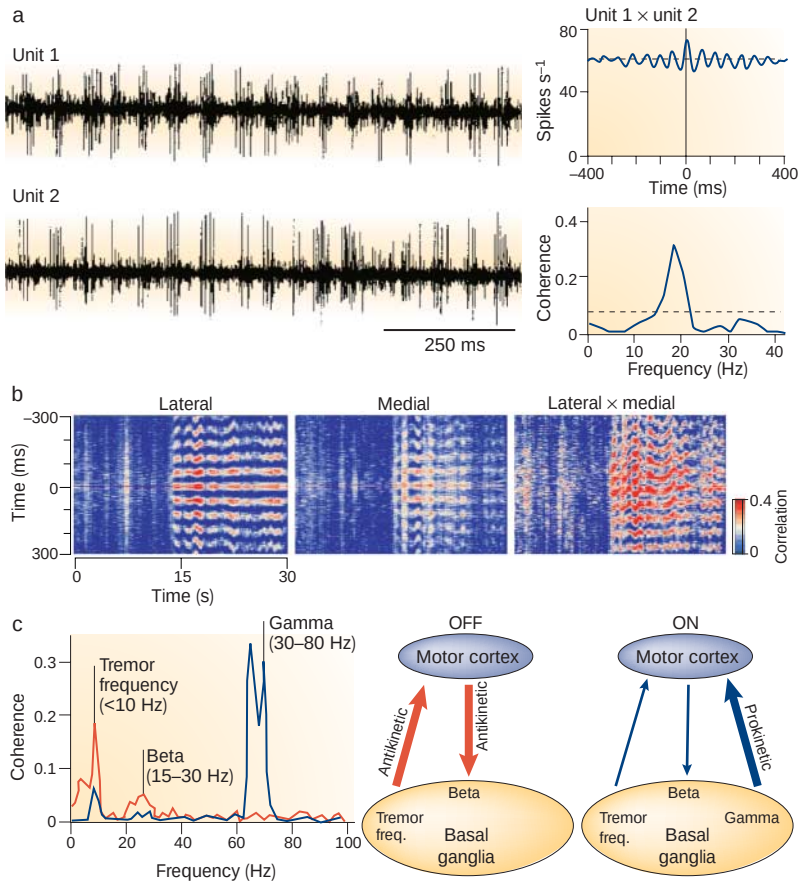


Figure 1 | **Multisite recordings help to elucidate the pathophysiology of basal ganglia disorders. a** | Fast oscillations in the subthalamic nucleus (STN) of a patient with Parkinson's disease (PD) who showed resting tremor. Left, recordings of two synchronously firing cells. Right, peaks in the CROSS-CORRELOGRAM (top) and coherence function (bottom) indicate synchronized oscillation in the beta band (15–30 Hz). **b** | Synchronized beta-band oscillations in a patient with PD but without tremor. Unit recordings were made from the STN using the 'Ben's gun' arrangement (BOX 1). The plots show sliding window autocorrelograms for two of the electrodes (lateral, medial) and the time course of the cross-correlation (lateral x medial). Recording electrodes were separated by 4 mm. Red indicates positive correlation peaks. Note the sudden onset of a synchronized beta oscillation. **c** | Dopamine-dependent changes in coherence between the globus pallidus (GP) and cortex in patients with PD. Left, coherence between the GP and cortex was measured during two different states: OFF levodopa (red) and ON levodopa (blue). In the OFF state, coupling between the GP and cortex is dominated by activity at tremor frequencies (<10 Hz) and in the beta band. In the ON state, there is strong coupling in the gamma band around 60–70 Hz. Right, schematic summary of the direction of interactions in the different frequency bands. Interactions at low frequencies are presumed to be akinetic, whereas high-frequency interactions correlate with enhanced capacity for movement. Panel **a** adapted, with permission, from REF. 16 © (2000) Society for Neuroscience; panel **b** shows unpublished data from C.K.E.M., W. Hamel, C. Buhmann, J. A. Koeppen, G. Engler, U. Hidding, C. Weiller, M. Westphal, D. Müller, H. Bergman and A.K.E.; panel **c** adapted, with permission, from REF. 36 © (2002) Movement Disorders Society.

Pathophysiological studies. Single-unit activity related to FOCAL EPILEPSY has been investigated in the human temporal cortex since the 1950s (REF. 47) (TIMELINE). In subsequent years, series of recordings of single-cell activity were directed at understanding the electrophysiological events that underlie focal epilepsy and at comparing the results from human epileptic neurons with those from animal models[48–51]. Those studies have characterized neuronal burst-firing patterns in human epileptic foci and have investigated the relationship between single-unit firing and population activity as measured by LFP or ELECTROCORTICOGRAPHIC recordings. They showed that at the onset of epileptic seizures, cells begin to synchronize and start phase-locking to the epileptic population spike that is visible in the LFP[51]. Interestingly, this can involve neurons that show normal firing patterns during seizure-free epochs[51]. A detailed discussion of pathophysiological findings and their implications for unravelling the mechanisms of epilepsy is beyond the scope of this article (for recent reviews, see REFS 53,54).

Single-cell recordings and language. Resecting an epileptic focus requires the removal of a small amount of overlying non-epileptogenic cortex, typically from the anterior temporal lobe[55,56] (FIG. 2a). This means that it is possible to record from apparently normal temporal cortex, although the recordings might be influenced by more widespread effects of the patient's epilepsy. As recordings in the lateral temporal lobe are usually confined to tissue that is subsequently resected, they do not include cortical sites that have been identified as essential for language, usually by intraoperative electrical stimulation mapping[57]. Nonetheless, recordings from this tissue provide interesting insights into language processing[58–66]. A large proportion of randomly sampled neurons in nonessential areas of temporal cortex show statistically significant changes in their activity during language tasks such as object naming or text reading[58–62]. So, the neural networks that are involved in language extend beyond 'essential' areas whose loss would lead to deficits in language processing. Single-cell recordings show that nearly all neurons in the superior temporal gyrus respond during listening, often with responses that are specifically related to certain combinations of consonants, indicating that they are involved in the categorization of verbal signals (FIG. 2b). Other neurons show specificity for word length or syllable structure[65]. In the same region, many cells also respond specifically to acoustic features during speech production by the patient[66]. In the middle and inferior temporal gyrus, more neurons responded to the patient's voice than to other voices[66].

Such studies have found no significant differences between the left and right hemispheres in the proportion of neurons whose activity changes during a language task, despite the fact that most subjects show hemispheric dominance for language on the WADA TEST. However, during verbal tasks, neurons in the dominant hemisphere changed their activity earlier than those in the non-dominant hemisphere and showed relative inhibition compared with activity during control tasks. By contrast, neurons in the non-dominant hemisphere changed their activity earlier and showed relative inhibition during nonverbal tasks[61,62,67]. These results indicate that, in the anterior temporal lobe, hemispheric dominance is reflected in earlier activity changes and in greater inhibition during tasks that are lateralized to that hemisphere. They also shed light on the task-specificity of cells. When several language functions were assessed during recording from the same neurons, most cells changed their activity for only one of the sampled behaviours (for example, naming or reading, but not both)[59,61]. Moreover, neighbouring neurons were often

WADA TEST
Injection of an anaesthetic (such as amobarbital) into the left or right internal carotid artery, which allows researchers to test the cognitive abilities of one cerebral hemisphere in isolation.

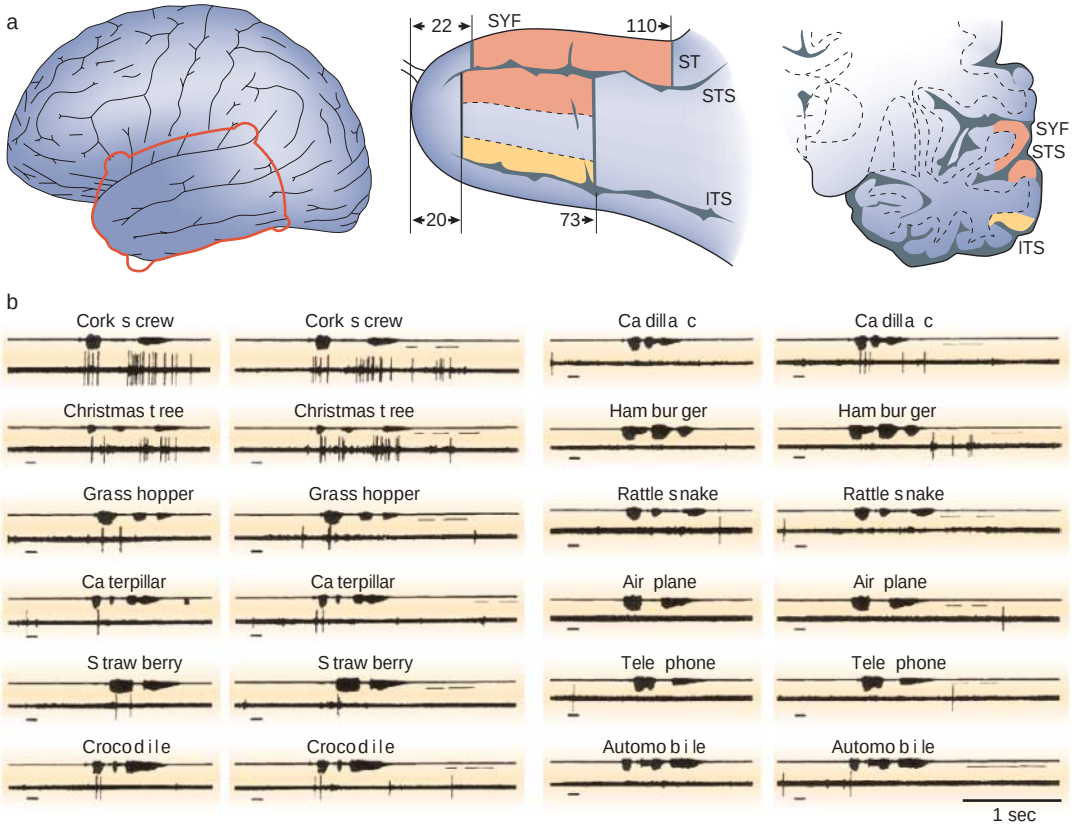


Figure 2 | **Single-unit recordings in the lateral temporal lobe probe language-related capacities. a** | The left panel shows the region of human temporal lobe where microelectrode recordings were obtained. The outline demarcates the craniotomy. The anterior and posterior limits of the recordings (in millimetres from the temporal tip) are shown in the middle panel. Yellow indicates the region where single-cell responses that differentiate individual stages of an explicit memory task occur significantly more often[56]. The orange region is where activity related to recognition and implicit memory occurs with high incidence[56]. A schematic coronal section through the anterior temporal lobe is shown on the right. ITS, inferior temporal sulcus; ST, superior temporal gyrus; STS, superior temporal sulcus; SYF, sylvian fissure. **b** | Activity of a neuron in the right ST when listening to a set of multisyllable words, each item being repeated twice. Specific patterns of activity occur in temporal lobe neurons with perception of specific words. Each record shows the audio signal (top) and the single-cell activity (bottom). The short line on the left of each record indicates a 1000-Hz tone that preceded each word. Thin horizontal lines under the audio trace demarcate a time period in which the patient was repeating the respective word. Note that similar patterns of activity are generated on both presentations of each item. The cell responds only in the trials illustrated in the left half of the panel, but not in the trials shown on the right, indicating a specificity for certain phonemes. Panel **a** adapted, with permission, from *Nature Neuroscience* REF. 56 © (2002) Macmillan Magazines Ltd; panel **b** modified, with permission, from REF. 65 © (1989) Springer-Verlag.

related to different aspects of language. So different networks for different functions might be interlaced in the same region, but not compartmentalized in separate columns.

Relation to memory. The lateral temporal cortex is also involved in learning and in declarative memory[68,69]. When microelectrode recordings are used to compare memory encoding of items with identification of the same items, 50–70% of anterior temporal lobe neurons show significant changes in frequency of activity[56,58–60], even though the only difference between identification and memory encoding is the instruction to remember the item. In most cells, activity is greater during memory encoding. Generally, those memory-related changes were widely distributed in both hemispheres. However, when memory encoding for objects was assessed with pictures, text or auditory words, neurons in the hemisphere that was dominant for language changed their activity irrespective of the stimulus modality, whereas cells in the non-dominant hemisphere reacted only to single modalities[56]. Different memory-related neural activation patterns were found to localize to different regions. In the dominant hemisphere, responses showed sustained activity throughout encoding, storage and recall, possibly reflecting attentional mechanisms[56,59]. Activity that was confined to only one stage of the memory task — encoding, storage or recall — was more likely in recordings from the inferior and basal temporal cortex[56] (FIG. 2a). This activity probably reflects processes that are active during each memory stage.

Microelectrode studies in the temporal lobe have also identified correlates of other types of memory, such as implicit memory (assessed by PRIMING) and recognition memory[56]. Neurons with activity related to these memory types were predominantly found in the superior

PRIMING
The facilitation of recognition, reproduction or biases in selection of stimuli that have recently been perceived.

temporal gyrus (FIG. 2a), indicating that this region is involved in procedural and perceptual memory. Neurons in the same region can also signal whether performance on a memory task is correct or incorrect[70]. Two studies have looked at the cellular correlates of learning in word-pair association tasks[71,72]. These recordings identified cells that showed reduced activity during word reading and increased activity for recent verbal memory. The cells showed specifically enhanced activity for those word-pair associations that were learned, and were more active in patients that rapidly acquired the associations. Once a word pair had been learned, the activity of these neurons rapidly declined on subsequent 'overlearned' correct production of the learned pairings. Such cells (called 'association neurons') could be causally involved in human associative learning.

LFP recordings from the neocortex. In patients with epilepsy, the origin of seizures is sometimes located by using subdurally implanted electrode arrays to continuously monitor epileptogenic activity[73] (BOX 1). Subdural electrodes have lower spatial resolution than microelectrodes, and they are sensitive only to coherent fluctuations and synchronized activity in local cell populations. However, they make it possible to observe interactions in large cell assemblies, which usually span several cortical areas. These electrocorticographic recordings are also better than EEGs at sampling high-frequency signal components such as those in the gamma-frequency range, which are damped by the media around the brain. Therefore, such approaches have potential for investigating cortical function and dynamic neural processes.

Semichronic grid recordings from the cortical surface have confirmed results that were obtained earlier using non-invasive recordings[74,75], including MOVEMENT-RELATED DESYNCHRONIZATION in the alpha- (8–15-Hz) and beta-frequency ranges and movement-related synchronization in the gamma-frequency band over sensorimotor cortices[76–81]. Because the grid recordings have a higher spatial resolution and the signals are less blurred than in scalp recordings, the invasive approach makes it possible to use spectral analysis as a tool for mapping brain function (FIG. 3). This approach uses both the amplitude and timecourse of event-related power changes[77,78]. Interestingly, mapping with high-frequency components delivers more specific results than with alpha-band responses[77,78,82] (FIG. 3a). Intracranial studies consistently report gamma-band activity with a much better signal-to-noise ratio than scalp recordings, and they reveal task-related changes at higher gamma-band frequencies[78,81] than most EEG studies, which typically observe gamma-band activity around 40 Hz (REF. 46).

LFP recordings have also been used to study task-dependent coherence changes across separate grid electrodes[79,80] (FIG. 3b). During tasks that require a high degree of sensorimotor coordination, coherence in the gamma band is particularly pronounced between pre- and postcentral cortical sites. These data agree with the 'dynamic model' of motor function that was discussed above in the context of basal ganglia research[24,35,36,38], in which high-frequency coherence subserves normal motor function, whereas lower frequencies predominate during states of reduced movement. Moreover, these data support the theory, derived from studies in sensory systems, that signals in the gamma band are associated with cortical activation, focused attention and processes of multi-regional and multi-modal integration[44–46].

These types of study have also shown that auditory tasks[82] and language processing[83] can produce gamma-band enhancement, with specific gamma-band activity in response to PHONEMES or during word production. Such invasive recordings provide valuable information on the spatiotemporal dynamics of large neural assemblies. They also allow recording over several days from the same cell populations, whereas neocortical single-cell recordings are typically carried out during acute surgery (for an exception, see REF. 84).

Probing the human medial temporal lobe

In studies of some patients with epilepsy, depth electrodes (BOX 1) have been used by surgically advancing them into the medial temporal lobe (MTL), which includes the hippocampus, amygdala and entorhinal and parahippocampal cortices, as well as into extra-temporal sites. Variations on this technique can allow semichronic recording (over a few days) of LFPs and single- or multi-unit activity, and even the combination of such recordings with microdialysis[85–88]. This technique allows unit activity to be monitored over several days, so that several sets of stimuli or behavioural protocols can be tested on the same cells. In addition, the behaviour of the same units can be studied both during seizures and in other states, such as wakefulness and different sleep stages[89].

Pathophysiological insights. Such recordings have provided valuable pathophysiological information. For example, they have shown that neurons in epileptic MTL regions have higher firing rates, more frequent burst discharges and stronger synchrony than neurons from non-epileptic regions. These differences are particularly pronounced during sleep, but are negligible if only data from wakefulness are considered[89]. This implies that levels of arousal should be considered when trying to identify pathological INTERICTAL ACTIVITY. Such data are also important because evidence relating to human interictal activity does not generally agree with physiological data from animal models[89]. From the viewpoint of cognitive neuroscience, such recording approaches provide a unique window for monitoring the activity of microcircuits and for studying memory formation, perceptual processing and even consciousness in the human brain[52,90,91].

Single-unit recordings and memory. Early single-unit recordings from the MTL showed that most cells in the hippocampus gave item-specific responses during word or picture recognition tasks[85,92]. However, many cells changed their stimulus-specificity during repeated performance of the task, indicating that neurons might be recruited only temporarily into a hippocampal assembly that encodes the stimulus. A larger data sample[86] revealed

MOVEMENT-RELATED DESYNCHRONIZATION
A decrease or increase in power in a certain frequency band shortly before or during the execution of a movement.

PHONEMES
Individual units of speech sound that combine to make words.

INTERICTAL ACTIVITY
Neural activity in an epileptogenic region in the time between two seizures.

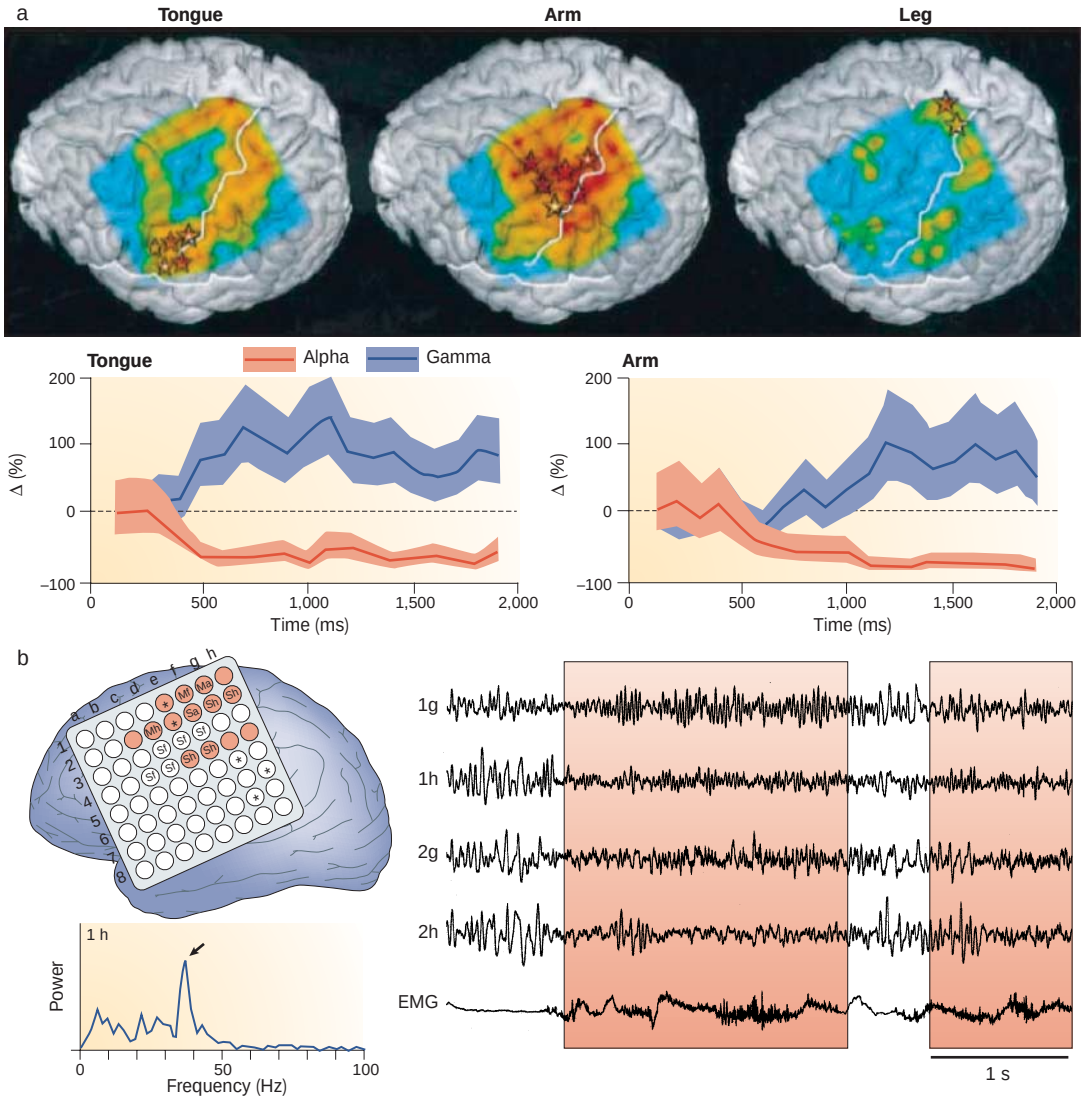


Figure 3 | **Invasive recordings reveal assembly dynamics in the human brain. a** | Topography of event-related gamma synchronization and alpha desynchronization (top). Data are shown separately for tongue (left), hand (middle) and foot movement (right). The extent of the recording grid is indicated in blue. Red–yellow colour indicates the amount of alpha desynchronization; stars mark sites with movement-related gamma synchronization. The topography of responses is more specific for the gamma than for the alpha band. Graphs show the time course of event-related changes in the alpha (red) and gamma band (blue) during tonically sustained tongue (left) or arm (right) movement. Δ(%), percent change relative to prestimulus baseline. **b** | Subdural recording during a difficult visuomotor coordination task[80]. The position of the recording grid is shown (upper left). Functional mapping by electrical stimulation identified some sites as motor (M) or sensory (S). Lowercase letters indicate somatic location: hand (h), arm (a), face (f). Sites with an asterisk were identified as epileptogenic. Orange circles indicate sites where movement-related coherence changes were analysed. Plots of activity recorded during the task are shown on the right. Movement episodes are indicated by shaded boxes and by electromyographic (EMG) activity (bottom trace). At electrodes 1g, 1h, 2g and 2h, 30–40-Hz oscillations occur during movement. Graph (lower left) shows power spectrum of the signal at electrode 1h. Note the prominent peak (arrow) close to 40 Hz. Panel **a** modified, with permission, from REF. 78 © (1998) Oxford University Press; panel **b** adapted, with permission, from REF. 80 © (2001) Elsevier Sciences Ltd.

specific activation of cells during behavioural responses to target stimuli, occurring at about the same time as the P3 COMPONENT recorded in the depth LFP. Such responses might reflect the matching of target stimuli with information held in working memory[86]. Surprisingly, these studies found no evidence for an association between neural firing patterns and performance on the memory task, despite the key role of the hippocampus and associated structures in declarative memory[93].

Another set of studies used semichronic recordings from the MTL and from extratemporal sites during different memory tasks[94–96]. During a task that involved recognition of pictures of faces and objects, a substantial fraction of cells in the hippocampus and amygdala responded to specific conjunctions of features[94]. The data were compatible with a sparsely coded, distributed representation of stimuli in the MTL. Memory-related firing patterns in the hippocampus and entorhinal cortex

P3 COMPONENT
A positive electroencephalogram wave that appears 300–500 ms after a salient or novel stimulus that has attracted the subject's attention.

showed interesting differences during a word-pair association task[95]. During the task, firing rates decreased in most hippocampal cells but increased in most entorhinal neurons. This study also provided the first evidence for a correlation between neural firing and memory performance, and this relationship differed between hippocampal neurons and entorhinal cortical cells. In the hippocampus, activity during encoding predicted whether subjects later remembered word pairs, whereas in the entorhinal cortex performance was predicted by activity during retrieval. Hippocampal responses to subsequently forgotten word pairs were higher than they were to remembered items, but the equivalent responses in the entorhinal cortex were lower[95]. These findings indicate that different MTL regions might contribute differently to memory. Such region-specific differences in firing patterns during encoding and recall were also found in memory for faces and objects[96]. Between 20 and 30% of neurons in the hippocampus, entorhinal cortex and amygdala change their firing rate significantly in response to faces or objects, with most cells being specific for one or the other. Amygdala neurons usually show increases in activity during encoding of stimuli, whereas hippocampal neurons typically show inhibition during encoding and recognition of faces[96]. Recently, the finding that MTL neurons can discriminate correct from incorrect object identification has been confirmed, but the correlation to memory performance was not found, possibly owing to a small sample size[70].

Human spatial navigation. The 'place cells' of the hippocampus constitute one of the most striking correlations between neural activity and behaviour in mammals[97]. Recordings from the hippocampus and surrounding structures were used to look for place-related activity in patients playing a computer game in which they had to navigate round a virtual town[98] (FIG. 4a). Many of the recorded cells responded either to specific spatial locations (place cells) or to views of task-relevant landmarks (view cells). Place cells were more frequent in the hippocampus than in the parahippocampal region, whereas view cells showed the opposite distribution. A subset of place cells was modulated by the goal of the navigation, responding when a particular target building appeared at a specific location but not when other virtual houses were encountered there[98]. As well as revealing mechanisms of spatial representation in the human brain, these data establish a link to animal experiments, as place cell responses have been studied most extensively in the rat hippocampus[97]. Although some components of the rat cellular navigational system seem to be conserved in humans, other aspects might be different because the neurons also respond to view- and goal-related information.

Perception and awareness. Although the MTL is not essential for perception, the human hippocampus and associated structures are important for the encoding and retrieval of conscious percepts. A number of investigations of MTL activity have addressed perceptual categorization, selection and awareness[99–101]. Kreiman and colleagues[99] tested the selectivity of cells for object categories such as faces, household objects, scenes, animals or cars. About 15% of the cells tested showed category-specific visual responses, but did not discriminate between different items within a category (FIG. 4b). These data indicate that MTL neurons are involved in categorizing visual stimuli and that this information might be used for transforming percepts into declarative memory. The same group found single neurons in several MTL structures that selectively altered their firing rate during imagery[100]. These imagery responses were category specific, and most of the cells showed the same category specificity for imagined and for real visual stimuli, indicating that there might be a common neural pathway for processing of visual input and visual recall. These data show that activity in the MTL represents the contents of perception rather than the physical stimulus itself and, therefore, reflects the results of perceptual selection processes that control access to conscious awareness[91,102,103].

This conclusion is also supported by a study[101] that used the 'flash-suppression' protocol to examine neural responses in the MTL (FIG. 4c). In this protocol, visual stimuli are presented separately and with temporal offset to the subject's left and right eye. If only one image is presented, this will be processed to reach visual awareness. Flashing another stimulus into the other eye 1 second later suppresses the formerly perceived stimulus; instead, the new image becomes perceptually dominant[101,104] (FIG. 4c). Two-thirds of the visually responsive MTL cells followed the perceptual alterations rather than the retinal input (FIG. 4c), indicating that activity in this region directly correlates with phenomenal visual experience. The data agree with similar experiments in macaque monkeys[104].

LFP data from the MTL. Depth electrodes have been used to investigate EVENT-RELATED POTENTIALS (ERPs) during cognitive tasks. For instance, the scalp P3 ERP component is assumed to reflect the closure of cognitive processing of a salient event and the updating of information held in working memory[105]. This component is observed in tasks that involve the detection of deviant stimuli among repetitive series of non-target stimuli. It is evoked when the target stimulus has captured the subject's attention and reached awareness[106]. Depth recordings showed that P3 generators are located in the hippocampus[107], the superior temporal sulcus and the amygdala[108], indicating that a network of limbic, memory and multimodal association structures might be involved in the processes that are reflected in this ERP component.

Depth electrodes have also been used to characterize fast rhythms in humans. Using such electrodes, human gamma-band rhythms were first recorded in the visual cortex[109]. Applying the same technique to the MTL, recent studies show enhanced gamma-band activity in LFPs recorded from the surface of the parahippocampal gyrus[110]. The rhythms are most prominent in the waking state, but also present during natural sleep[111]. Recent studies have recorded 'ripple oscillations' (100–200 Hz)

EVENT-RELATED POTENTIAL
Phase-locked electroencephalogram activity, obtained by averaging data segments recorded after presentation of a stimulus.

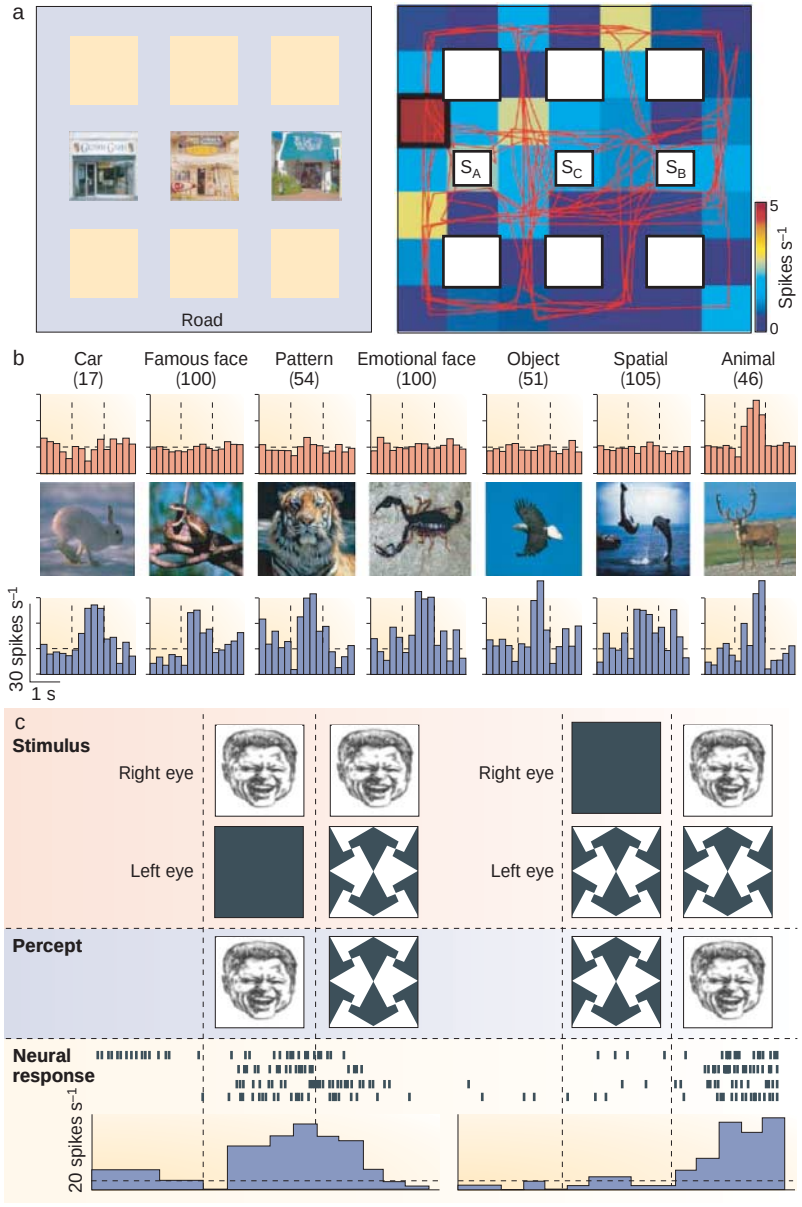


Figure 4 | **Recordings in the medial temporal lobe (MTL) yield insights into perceptual and memory functions. a** | The human hippocampus contains place cells. Individuals had to explore a virtual town and navigate to three target locations (left). The panel on the right shows a firing-rate map of a place-responsive hippocampal cell. Letters indicate shop locations; white squares indicate non-target buildings; the red line is the subject's trajectory. Colours show firing rate (spikes s^{-1}), which was maximal in the red square with black outline. **b** | Category-specific visual response in the entorhinal cortex. Top graphs show the average response of the cell to different stimulus categories. The number of items tested is in parentheses. Vertical dashed lines show stimulus onset and offset; horizontal dashed line indicates the average firing rate over the whole experiment. This entorhinal cortex cell responds specifically to images of animals. Bottom graphs show responses to seven pictures of animals. The cell responses do not seem to differ between different animals. **c** | Recordings from a neuron in the amygdala that follows the subjective percept in a flash-suppression experiment. The response from the cell was greatest when the subject was shown images of Bill Clinton. The raster plots and firing-rate histograms (bottom) show the response of the recorded cell after presentation of the stimulus (top). The percept, as experienced by the patient, is shown in the middle. After showing the image of Bill Clinton monocularly to the right eye for one second, a black-and-white pattern is flashed to the left eye, suppressing the percept of Bill Clinton (left panels). In the reverse situation (right panels), the black-and-white pattern is presented first and then perceptually suppressed by flashing the picture of Bill Clinton. The cell responds only when Bill Clinton is perceived. Panel **a** adapted, with permission, from *Nature* REF. 98 © (2003) Macmillan Magazines Ltd; panel **b** modified, with permission, from *Nature Neuroscience* REF. 99 © (2000) Macmillan Magazines Ltd; panel **c** adapted, with permission, from REF. 101 © (2002) National Academy of Sciences USA.

and 'fast ripples' (250–500 Hz) in both hippocampal and entorhinal cortex[112,113]. Ripple oscillations occur physiologically during both sleep and waking and have been related to memory[114], whereas fast ripples seem to be related to epileptogenesis[113]. Coherence between MTL structures in the high-frequency range is related to memory functions[115–117]. Coupling between the entorhinal cortex and hippocampus is enhanced in the gamma-band range during successful encoding, indicating that these structures might cooperate by dynamic synchronization during the formation of declarative memories[115]. This coupling is accompanied by enhanced coherence in the theta band[116] and is reduced during sleep[117]. Another behavioural correlate of high-frequency activity in the MTL was found in LFPs that were semichronically recorded from the amygdala. Strong gamma-band responses occurred during the processing of aversive, but not pleasant or neutral, stimuli[118]. These studies provide evidence that synchronization of neural assemblies in the MTL is relevant to cognitive processes such as memory formation and recall.

Conclusions and future perspectives

The invasive recording techniques that we have discussed allow neural activity to be sampled at different spatial scales, ranging from single- and multi-unit activity to local or more distributed cell assemblies (BOX 1). Single-cell recordings allow researchers to investigate neural coding, the specificity and tuning of neural responses, and neural topographies and maps. But it is also important to study how neurons interact to form functionally coherent cell assemblies that allow distributed representations[44,45,119]. The evidence indicates that such codes exist in the human brain, and that the 'signatures' of assembly formation, such as task-dependent neural synchronization, are similar to those found in the brains of animals[119]. Parallel recordings with multiple microelectrodes — already used in the basal ganglia and MTL — will be essential for studying assembly dynamics in the human cortex. LFP recordings can also reveal subtle and specific spatiotemporal interactions in large multiregional assemblies. Future work should aim to combine these different approaches into a technology that allows both multi-scale and multi-region recording over days, weeks or even years[87,120,121].

Future applications of invasive techniques will probably include extensions of current approaches as well as entirely new types of medical intervention. New developments might include, in addition to improved mapping techniques, the application of DBS to diseases such as OBSESSIVE-COMPULSIVE DISORDERS and certain types of epilepsy[122,123], and the implementation of demand-controlled pacemakers[124] to replace the continuous stimulation of target neurons. In the field of epilepsy, the development of real-time seizure prediction using signals from implanted electrodes is under way[125]. Such predictive signals could be used for closed-loop triggering of electrical stimulation or focal drug infusion to prevent epileptic attacks.

A challenging new line of research concerns the development of brain–computer interfaces (BCIs), which use neural signals recorded from a patient to control a screen cursor, a robot (see REFS 126–128), or even the limbs of a paralysed patient (by stimulating muscles electrically)[129]. The clinical goal of such attempts is to allow severely disabled patients to communicate and to control devices. Another ambitious aim is to build neuroprosthetic devices that can stimulate or 'read' neural activity patterns, with the intention being to use them as replacements for lost sensory organs or limbs. Current non-invasive BCIs use signals extracted from scalp EEGs[126,127] or changes in the haemodynamic signal measured by functional magnetic resonance imaging[130,131]. However, the capacity for information of such BCIs is limited, and significant improvements might be achieved by recording the command signals directly from the brain. In non-human primates, multielectrode recording of assemblies in motor cortex can be used to predict limb movements and to control robotic arms[132–134]. In humans, studies now suggest that unit activity can potentially be used to drive a BCI[135,136]. However, such approaches suffer from biocompatibility issues and loss of signal quality over time[128]. Electrocorticographic LFP recordings might therefore show promise[137–139]. A recent study[139] used event-related beta-desynchronization and gamma-synchronization at specific grid electrodes to drive the BCI, and showed rapid learning and high specificity of the recorded signals in the context of the task. The development and use of BCIs has important clinical implications, but could also provide insight into neural processing and plasticity. Arguably, neuroprosthetic interfaces will be one of the future touchstones for invasive approaches to the human brain — technologically and ethically.

Invasive recordings seem indispensable, both with respect to biomedical applications and from the viewpoint of basic research. For the time being, they provide the only access to the human brain at cellular resolution. Invasive methods allow us to extend neurophysiological studies done in animals and to address cognitive functions that are specific to humans, such as language or imagery. As discussed above, these methods even make it possible to investigate single-cell correlates of subjective experience, thereby invading territories previously reserved for philosophy and the humanities. Therefore, invasive recordings are not only relevant for developing new neuroengineering techniques, but they might also substantially contribute to our future understanding of the biology of the human mind.

OBSESSIVE-COMPULSIVE DISORDER
A neuropsychiatric disorder that leads to an abnormal degree of disturbing and intrusive thoughts and impulses, as well as compulsive behaviours.

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Competing interests statement

The authors declare no competing financial interests.

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