Oscillatory multiplexing of population codes for selective communication in the mammalian brain

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Abstract

Mammalian brains exhibit population oscillations whose structures vary in time and space according to behavioural state. A proposed function of these oscillations is to control the flow of signals among anatomically connected networks. However, the nature of neural coding that may support oscillatory selective communication has received relatively little attention. Here we consider the role of multiplexing, whereby multiple information streams share a common neural substrate. We suggest that multiplexing implemented through periodic modulation of firing rate population codes enables flexible reconfiguration of effective connectivity among brain areas.

Periodic synchronisation of neuronal spiking is a striking feature of brain activity, occurring both within and across regions. The spatiotemporal structures of these network oscillations often vary systematically with behavioural and cognitive tasks. At the cellular and network level the mechanisms underlying periodic activity in neural circuits are increasingly well understood[1-5] (Box 1). Relatively less is known about the computational roles that oscillatory dynamics play in high-level processes, although a prominent hypothesis is that a function of network oscillations is to control the flow of information through anatomical pathways, thus flexibly modulating effective connectivity among local networks[6-10]. Such mechanisms may play an important role in supporting flexible and context-dependent behaviour; because local circuits perform highly specialised computations or process information from different sources, distinct behavioural tasks require different combinations of regions to work together, calling for different patterns of information flow through long-range anatomical connections. For example, information about the target location for a movement may come from distinct sensory modalities or be recalled from memory. The same motor output must therefore utilise information represented in different brain areas. Conversely, a given sensory cue may be used to guide different motor actions such as a reaching limb movement or a saccade, or a purely cognitive action such as updating information held in short-term memory. In each of these cases information from the relevant sensory area must be accessed by distinct downstream targets.

There are of course numerous mechanisms that can modify the flow of information through neural circuits without relying on population oscillations, such as synaptic plasticity across a range of timescales[11] and plasticity of intrinsic neuronal excitability[12]. Additionally, network-level mechanisms have been proposed for routing asynchronous firing rate

signals[13-15]. However, as we summarise below, recent computational work has shown that oscillations can, in principle, support flexible and selective communication, and experimental evidence for task-dependent modulation of oscillatory activity provides compelling, albeit correlational, evidence for such a role.

Another long-standing hypothesis about the functional role of network oscillations is that they serve as a mechanism for multiplexed neural coding[10,16-19]. Multiplexing is the process of combining multiple signals for transmission through a single communication channel, in such a way that the distinct components can be independently recovered from the transmitted signal. In telecommunication systems a principal application of multiplexing is to support selective communication in situations where a single signal source communicates with multiple receivers, or conversely multiple sources with a single receiver, as exemplified by the reciprocal selective communication between a base station and mobile phones. In neuroscience, by contrast, multiplexed coding has been discussed primarily as a solution to problems of information representation, including binding features of sensory scenes corresponding to individual objects[17], increasing the capacity or robustness of sensory neural codes[18], or representing multi-item lists or sequences[16,20,21].

With some exceptions[10,22], there has been little explicit discussion of what role, if any, multiplexing plays in the hypothesis that network oscillations implement selective neural communication. This is the focus of the first section of this review, in which we argue that multiplexing plays a necessary role in such mechanisms. In the second section we suggest that multiplexing may be implemented through multiplicative modulation of firing rate population codes. This proposal may reconcile the abundant evidence for firing-rate population coding with data implicating changes in oscillatory patterning of activity in controlling information flow.

The role of multiplexing in selective oscillatory communication

All neuronal communication is in a trivial sense 'selective' because it is constrained by anatomical connectivity. In the discussion that follows we use the term to describe mechanisms that permit communication that is more selective than that implied by the underlying anatomical connectivity. Defined thus, selective communication may occur in either convergent or divergent pathways, both of which are widespread in long-range connections among both cortical and sub-cortical networks.

Information flow through a convergent pathway may be termed selective if a network receiving several inputs can respond preferentially to one or more of the inputs even *after* they have been combined by spatial overlap of synaptic activity. We will focus primarily on the simplest case: setting the gain for one of the inputs to one and for all the other inputs to zero. Such 'hard switching'[14] could be advantageous, for instance, if only one input is behaviourally relevant (the 'target' input), while all others ('distractor' inputs) should be ignored. In practice, control of effective connectivity may typically be subtler, but this limiting case is fundamental for understanding selective communication more generally.

Selective communication in a divergent pathway implies that a single population of neurons sends distinct signals to different projection targets. These signals could be qualitatively

different, or the same signal with independent control of the gain for each of the projections. We will focus primarily on the latter, and in particular on the limiting case where the signal is turned on or off for different targets.

Selective communication in either convergent or divergent pathways requires multiplexing because in both cases a single spatio-temporal pattern of spike activity must carry multiple independently accessible information channels. In a convergent pathway it is the combined presynaptic activity in the spatially overlapping convergent inputs that must implement a form of multiplexing. If there is no algorithmic operation that can separate out information about a specific component of the combined input from other converging inputs, the receiving network cannot respond differentially to that component, no matter what dynamics it implements. For separate components of a convergent input to be differentially processed, their activity must therefore be structured such that they encode their signal into separate information channels in their combined activity. Similarly, for selective communication in a divergent pathway, different projection targets must be able to read out different signals from the same pattern of activity. This requires that the spatiotemporal pattern of spiking in the projecting network contain separate information channels that can be accessed by the different projection targets.

To understand how oscillatory mechanisms for selective communication may operate we must therefore consider the coding schemes used to implement the required multiplexing, the algorithmic operations that support demultiplexing, and the implementation of both through neural dynamics.

Multiplexing population codes through multiplicative modulation

There is extensive evidence that spatial patterns of firing rates distributed across populations of neurons are an important component of information representation in mammalian brains[23]. We therefore focus on how network oscillations can extend firing rate population coding to support multiplexing and hence selective communication. As such, this review does not discuss phase codes or other schemes in which the precise timing of spikes encodes the value of stimuli, although phase of firing does play an important alternative role in our proposals. See ref. [18] for a recent discussion of neuronal multiplexing using phase codes, and ref. [10] for a selective communication scheme which relies exclusively on spike timing and not firing rates to encode information.

Rate coding requires that neuronal firing rates vary systematically with the signal to be encoded, typically characterised through neuronal tuning curves. The presence of oscillatory activity by definition indicates that instantaneous neuronal firing rates are also periodically modulated. The nature of the interaction between these two influences on instantaneous firing rate is central to the multiplexing framework outlined here. We suggest that approximately multiplicative oscillatory modulation of firing rate population codes is used to multiplex neural signals (Fig. 1). Such multiplicative modulation takes the form:

$$R_i = P_i\left(S\right)\ m\left(t\right)$$

Where R_i is the instantaneous firing rate of neuron i, $P_i(S)$ is the tuning curve of neuron i with respect to the stimulus S, and $m(t)$ is an oscillatory modulation of firing rates common across the ensemble of neurons forming a coding population. This coding scheme posits a division of labour between the population code, i.e. the spatial pattern of average firing rates over the oscillation cycle, which represents the value of the signal, and the oscillatory modulation which acts as a form of meta-data allowing the signal to be distinguished from those with different modulations; and hence selectively or differentially processed. A separation of timescales is also implicit in this coding scheme because the stimulus, and hence the population code, must vary on a slower timescale than the oscillatory modulation. This is because operations that can selectively read out these codes, discussed below, obtain at most one sample of the encoded signal per cycle of the oscillation, and hence to avoid aliasing, the signal must not vary at frequencies higher than half that of the oscillation[24].

Multiplicative modulation supports multiplexing because algorithmic operations exist that can selectively recover signals with a given modulation while ignoring signals with different modulations, even when these signals are summed together. The question of how modulated population codes can be selectively read out or demultiplexed can be usefully addressed at both the algorithmic and implementational levels[25]: at the algorithmic level by identifying what mathematical operations on a pattern of spike activity allow population codes with different modulations to be selectively recovered, and at the implementational level by addressing what biophysical mechanisms may perform such operations in neural systems.

Time- and frequency-division multiplexing

Qualitatively different multiplexing schemes can be implemented by segregating signals by phase or frequency of oscillation. Segregation of signals into separate phases of a repeating cycle is termed time-division multiplexing (TDM) while segregation into different frequency bands is termed frequency-division multiplexing (FDM). Both forms of multiplexing are widely used in telecommunication, and in a neural context both can be implemented through multiplicative modulation of population-coded signals.

To multiplex population codes using time division, the activity contributing to each code must be modulated relative to a common oscillation, each at a different phase, such that each is active at a different time during the oscillation cycle. This is illustrated in Fig. 2a in a convergent pathway, where different input populations are active at different phases. Selectively recovering the individual signals is straightforward because they are active at different times. A simple algorithmic operation is to multiply the combined activity by a time-varying gain which is non-zero only when the target input is active and the other inputs inactive, and then integrate over time[26] (Fig. 2a). As long as the temporal overlap of the separate input components is low, the fidelity achieved by this readout is comparable to that achieved in the absence of distracting inputs because only the target signal contributes to the output.

Implementation of this readout requires periodic modulation of gain in the receiving network, phase-locked to the target input. Network oscillations can modulate the gain of neuronal responses to external inputs, and synchronised oscillation between a sending and

receiving region has previously been proposed as a fundamental mechanism for selectively enhancing communication between networks[9,27]. Periodic modulation of gain across the oscillation cycle could occur through modulation of the membrane potential distribution, the level of shunting inhibition[28] or synaptic noise[29], in turn due to the periodic activity of local interneuronal populations. Changes in neuromodulatory or GABAergic tone across the oscillation cycle may also influence the effective gain for inputs through presynaptic modulation of transmission at afferent synapses[30]. Computational studies confirm that periodic input applied to a population of cells can enhance the representation of a target input relative to phase-separated distracting input by biasing excitability as a function of the phase of the input activity[31-33].

While it is intuitive that coherent gain modulation can selectively read out signals that are segregated into distinct phases of an oscillation, it is perhaps less obvious that the same mechanism can in principle also extract signals in an FDM scheme, allowing selective readout of signals that are segregated into different frequency bands[26] (Fig. 2b). This is possible because approximately sinusoidal gain modulation at one frequency has no effect on the average gain experienced by an input modulated sinusoidally at a different frequency, since periods of heightened and reduced gain cancel out when averaged over a few cycles. Mathematically, sinusoidal gain modulation at one frequency does not affect the average gain for inputs whose firing rate is modulated at a different frequency because the two modulations are orthogonal under the overlap integral operation that constitutes the readout algorithm (Box 2).

Indeed, orthogonality plays a key role in both the TDM and FDM schemes outlined above. Both work by reproducing population codes, i.e. static or slowly varying patterns of average firing rate distributed across constituent neurons, selectively into specific components of the rapidly varying firing rate, but not into other orthogonal components which can hence be used as separate communication channels. In TDM the population code is reproduced selectively into the spatial pattern of activity at a given phase, but not at other phases. In FDM the population code is reproduced selectively into the envelope of fluctuations of the firing rate in a specific frequency band, but not in other frequencies. Note that this selective reproduction is not a generic feature common to any periodic modulation of activity, but rather a consequence of the multiplicative nature of the modulation. For example, in a network where oscillatory activity generated additive modulation of firing rates, the population code would be equally present in activity at any phase of the oscillation and the envelope of firing rate fluctuations at the oscillation frequency would be flat and uninformative.

Demultiplexing FDM population codes does not necessarily require knowledge of the phase of the target input's oscillation. It is sufficient to evaluate the spatial pattern of firing rate oscillation amplitude at the appropriate frequency[34]. This readout algorithm can be implemented by a pathway that performs band pass filtering followed by rectification (Fig. 2c). We implemented this in a biophysical model[34] where the band-pass filtering was performed by a network-level resonance[35] in a feed-forward inhibitory population and rectification by the spike threshold. Sub-threshold resonance in individual neurons is an

alternative biophysical mechanism which could implement the required band-pass filtering[22,34,36].

Beyond time and frequency division

Much recent interest has focused on cross-frequency coupling (CFC) between oscillations[37,19,38], and in particular on task dependent modulation of phase – phase CFC, i.e. systematic relationships between the phase of oscillations in different frequency bands, and phase – amplitude CFC, in which the amplitude of a high frequency oscillation is modulated by the phase of a low frequency oscillation. We will touch only briefly on what role CFC may play in a multiplexing framework employing modulated population codes because current data under-constrain which of different possible functions it may subserve. Phase – phase CFC seems most interpretable in a time-division framework in which channels are created by segregating activity with respect to the phase of multiple oscillations at different frequencies. Phase – amplitude CFC has possible interpretations in pure time-division, pure frequency-division, or in mixed multiplexing schemes utilising both time and frequency division principles. In pure time division, where separate channels are segregated by phase relative to a low frequency oscillation, a concurrent higher frequency oscillation could help segregate activity contributing to each channel if each is active on a separate cycle, as proposed by the 'theta – gamma' code[16,20] discussed further below. In a pure frequency division scheme, nesting of a high frequency oscillation within a lower frequency oscillation could be used to simultaneously reproduce a population code into both frequency bands[34]. Finally, in a multiplexing scheme combining time and frequency division principles, higher frequency oscillations could create frequency division sub-channels within time division channels segregated by the phase of a low frequency oscillation.

A more radical departure from the use of TDM or FDM principles is proposed by the influential communication through coherence (CTC) hypothesis[9]. CTC proposes that selective communication is achieved by coherence between oscillatory modulation of activity in a sending region and modulation of neuronal excitability in a receiving region, and conversely that communication is blocked by incoherence between such oscillations. (Because oscillations in the brain are typically irregular, incoherence does not require them to be separated in frequency.) There is substantial common ground between CTC and the selective communication framework outlined above; selective readout by gain modulation coherent with a target input is central to CTC, and although the nature of coding is less explicitly defined, a division of labour between spatial patterns of activity – used to encode information – and oscillatory modulation – used to define the communication channel – appears consistent with the CTC hypothesis.

However, the form of multiplexing implicitly underlying CTC is fundamentally distinct from either TDM or FDM. Consider the situation of a network receiving input from two afferent pathways, both oscillating in the same broad frequency band, incoherently with each other (Fig. 3a). The CTC hypothesis asserts that the receiving network can selectively respond to one of these inputs by oscillating coherently with it. However, the two inputs are neither consistently non-overlapping in time as in TDM, nor are they well segregated by frequency, as in FDM. This raises the questions whether CTC (henceforth used to describe

arrangements in which separate channels are defined by incoherent oscillations in the same broad frequency band) can actually work in principle (i.e. can accurate selective communication be achieved?), and if so what form of multiplexing it represents.

A partial answer to the first question is suggested by a recent computational study in which we evaluated how the structure of oscillatory activity across a set of converging input pathways determined the accuracy with which a 'target' input could be selectively read out by coherent gain modulation in the receiving network[26]. The structure of the model was as illustrated in Fig. 2, and the target and distracting inputs were either segregated using TDM or FDM, or oscillated incoherently in the same frequency band. The rate of information transmission was substantially reduced in the latter case because any pattern of gain modulation in the receiving network that was strongly driven by the target input incurred a substantial fluctuating drive from the distracting inputs as they drifted in and out of phase with the target (Fig. 3a). CTC only performed comparably with TDM or FDM multiplexing schemes in low firing rate regimes where stochastic spiking of individual neurons became a more significant source of noise than random fluctuations in overlap between the target and distracting inputs. Although we think it unlikely that mammalian brains operate in a firing rate regime where CTC is comparably efficient to schemes using TDM or FDM (see ref [26] for a quantitative discussion), this question can ultimately only be resolved with respect to a detailed quantitative picture of communication in specific systems.

With respect to the form of multiplexing underlying the CTC hypothesis, the closest analogy is with a scheme know as code division multiple access (CDMA, ref, [39]) used in digital telecommunication (see diagram; Fig 3b). In both the CTC hypothesis and CDMA the signal is modulated with a broadband time series – an irregular oscillation in the former case and a pseudorandom noise (PN) sequence in the latter. In both cases the modulations used by different channels overlap in time and frequency and are not coordinated with each other. As the PN sequences used to modulate different CDMA channels are not strictly orthogonal, some interference occurs between channels. However, despite this drawback, CDMA finds widespread use in wireless communication, in part due to the advantage that different sources do not need to be synchronised with each other as in time division schemes. However, this analogy risks overstating the practicality of CTC as a multiplexing scheme. Pseudorandom noise is not the same as broadband oscillation; while sequential bits of a PN sequence are uncorrelated, the phase of even a broadband oscillation is correlated over multiple cycles. Such autocorrelation in the modulations will reduce how quickly distracting signals can be 'averaged out' from a target signal, and hence, compared with pseudorandom noise, broadband oscillations appear poorly suited for use as a modulation in spread-spectrum multiplexing.

In summary, oscillatory modulation of population-coded signals can in principle implement multiplexing and hence selective communication using time- or frequency- division principles, or a form of spread spectrum multiplexing using irregular oscillations. These different approaches may offer distinct trade-offs between communication accuracy and implementational complexity. TDM in principle offers zero crosstalk between channels if activity contributing to each is completely non-overlapping in time. Some crosstalk is inevitable in FDM because Poisson-like activity fluctuations that occur during network

states with irregular neuronal activity contain some power at all frequencies. However network architectures implementing FDM may be less complex because networks transmitting into different frequency channels do not need to be synchronised with each other, and selective readout can be implemented by simple filtering networks using resonant dynamics. Spread-spectrum multiplexing using irregular oscillations in the same frequency band appears to offer substantially worse signal to noise performance than TDM or FDM except in low firing rate regimes. Although separate sending networks do not need to be synchronised, unlike in FDM some external mechanism is still required to synchronise the receiving network with a target input.

Time-division multiplexing in the hippocampal system

We now turn to experimental evidence suggesting the use of oscillatory multiplexing. We focus on four oscillatory activity patterns observed in specific regions and behavioural states: (i) theta oscillations during navigation in rodent hippocampus, (ii) theta oscillations in primate cortex during working memory tasks, (iii) beta oscillations in cortico – basal ganglia circuits during action planning, and (iv) gamma oscillations in the early visual cortex in spatial attention tasks. The first is a system where the interaction between rate coding and oscillatory modulation of activity is uniquely well characterised and is highly suggestive of TDM. The second and third offer striking examples of task-dependent changes in the amplitude of oscillatory activity in narrow frequency bands across distributed networks, a possible signature of FDM-based selective communication. The fourth illustrates changes in inter-regional synchronisation of oscillation with apparently minimal changes in other aspects of oscillatory activity.

In a system using modulated population codes to implement multiplexing we expect to see that spatial patterns of firing rate are important carriers of information, but vary on a slow timescale relative to approximately multiplicative oscillatory modulation of activity. Additionally, because oscillatory modulation of firing rates acts as a carrier for information, the achievable signal to noise ratio strongly depends on the strength of modulation[26,34], with weak modulations resulting in the signal being drowned out by noise from stochastic spiking. Thus, efficient use of this coding scheme calls for strong oscillatory modulation of activity relative to the average firing rate.

Neural coding during theta oscillations in dorsal hippocampus appears consistent with these criteria. Firing rates vary systematically with the spatial position of the animal[40-44] (Fig. 4a), and with non-spatial behavioural variables[45-47]. Unit activity is strongly modulated as a function of theta phase, with the firing rate of many units dropping close to zero across a substantial portion of each cycle[42-44,48]. If the oscillatory modulation is approximately multiplicative, there should be an approximately linear relationship between the average firing rate of a cell across the theta cycle and the amplitude of modulation of its firing rate on that cycle. Although we are not aware of a systematic characterisation of this relationship, the activity of example units indicates that the difference in instantaneous firing rates between phases of maximum and minimum activity is substantially larger when the cycle average firing rate is high compared with when it is low[42-44,49] (Fig. 4b), consistent with prediction. Hippocampal activity also appears to respect a separation of timescales

between changes in firing rate due to changes in the encoded variables and oscillatory modulation of activity. This is suggested by the activity of place units on linear tracks, where the increase and decrease of firing rates as the animal traverses a place field takes place over a duration of order 5 – 15 theta cycles (Fig. 4b), depending on place field size and the animal's velocity[42,43,48]. Finally, the phase of peak firing of individual units precesses to earlier phases as the animal traverses the place field, such that distinct populations of cells are active at different times during the cycle[48,42,43,50,44,49] (Fig. 4c). This phenomenon is often termed sequence compression[42], as ensembles of place cells representing locations visited over a timescale of several seconds are active in a temporally compressed sequence on each theta cycle. Although sequence compression is best characterised in spatial navigation, sequential activation of units across the theta cycle has also been reported during non-spatial behaviours[51,52].

Time division multiplexing by theta oscillation phase has been proposed as a general mechanism for representing information with a naturally sequential or multipartite structure, including sequences of events forming episodic memories[21] and lists of items stored in short term memory[16]. Cross-frequency interactions may enhance the segregation of different items in a 'theta-gamma' code in which different neuronal ensembles spike on successive cycles of a gamma oscillation, with the sequence of items in the list repeated periodically at a slower theta frequency[20]. Theta phase segregation requires readout mechanisms that can selectively or differentially process spike activity dependent on its phase. As described above, periodic gain modulation in a downstream network is an effective selective readout algorithm for time-division multiplexed signals, and has been proposed in this context[31]. However, rather than supporting selective readout into patterns of activity in downstream populations, an important function of theta phase segregation may be to permit selective readout of activity at specific phases into patterns of synaptic plasticity[21,42,53]. Hippocampal neurons *in vitro* exhibit spike-timing dependent plasticity[54,55] (STDP), whereby a presynaptic spike arriving shortly before a post synaptic spikes results in synaptic potentiation, but arriving shortly after leads to depression. Such a plasticity rule is thought to potentiate synapses from cells spiking at a given theta phase onto cells spiking at a somewhat later phase. STDP between sequentially activated cell assemblies is therefore a potentially powerful mechanism for the storage of navigation trajectories into directional patterns of connectivity between place cells, and potentially for storage of sequences of non-spatial events in episodic memory[21].

A separate hypothesised role of hippocampal theta in learning and memory is the creation of separate encoding and retrieval phases during the oscillation cycle, to prevent the retrieval of previously stored associations from interfering with the encoding of new memories[56]. This proposal stems from observations that the strength of input to the CA1 network from both the CA3 region and the entorhinal cortex is modulated by the theta cycle, with peak input from the two regions occurring at opposite phases. Additionally, both the strength and the sign of plasticity at synapses made by Schaffer collaterals from CA3 to CA1 pyramidal cells are modulated as a function of the phase of the theta oscillation[57-59]. Briefly stated, the idea is that during the encoding phase strong input from entorhinal cortex to CA1 and CA3 drives activity representing new external events in these networks, and heightened synaptic

plasticity at the Schaffer collateral synapses stores associations between events. Then, during the retrieval phase, weaker entorhinal input and stronger transmission from CA3 to CA1 permits the recall of previously stored associations. TDM plays a dual role in this proposal, supporting both selective communication – anti-phase modulation of entorhinal cortex and CA3 input allows CA1 to respond alternately to each in the encoding and recall phases – but also selective readout into patterns of synaptic weight through modulation of the gain for plasticity at Schaffer collateral synapses.

These different proposals emphasise some important points about multiplexed neural coding. Firstly, although we argue that multiplexing plays a necessary role in selective oscillatory communication, the converse is not true; there are certainly applications for multiplexed coding that are not selective communication in the sense of controlling signal flow between different regions. There are strong parallels for this in telecommunication where for example, multiplexing plays an essential role in allowing a base station to communicate selectively with multiple mobile phones, but additionally between a single phone and base station further multiplexing is used to create separate information channels for voice, data and other information streams. Secondly, while selective readout or demultiplexing is an essential complement to multiplexed coding, readout may be into patterns of modification of synaptic weights rather than activity in downstream populations. Thirdly, mechanisms for selective readout into downstream activity and into synaptic weight changes may be similar at an algorithmic level. Periodic modulation of the gain of neurons input – output transfer function can selectively readout multiplicatively modulated population codes into activity, while periodic modulation of the gain for plasticity can implement selective readout into patterns of synaptic modification.

Oscillation bursts: A signature of FDM?

Some of the most striking circumstantial evidence implicating oscillations in selective communication comes from evidence of transient bursts of oscillation, occurring synchronously across distributed networks and correlated with specific behavioural events. One such example occurs in working memory tasks in which the subject is presented with either a single stimulus or sequence of stimuli followed after a delay by a probe stimulus, and must indicate whether the probe matches the original stimulus. In humans performing such tasks, the amplitude of theta frequency oscillatory activity measured with intracranial electroencephalography (iEEG), changes dramatically during the trial in local regions of cortex, most prominently in occipital and parietal regions[60,61]. Many sites show an abrupt increase in theta power at trial onset that is sustained until it stops abruptly at trial offset. Trial to trial variability in amplitude changes in temporal and frontal regions predicted behavioural performance[62], implying a functional role for the oscillations. Recordings in area V4 of macaque cortex during delayed match to sample tasks show a transient burst of theta frequency oscillation in the local field potential (LFP) during the delay period, accompanied by phase locking of spikes to the LFP (ref. [63,64]) (Fig. 4e). Cortical theta oscillations associated with working memory in humans do not appear to form a single synchronised network as many sites oscillate independently[61]. However recordings in macaque showed enhanced phase synchronisation between V4 and lateral prefrontal cortex (LPFC) during the delay period, which was stronger on correct than incorrect trials[64],

indicating that in some cases oscillatory activity is synchronised between spatially separated sites, and implying that this coupling is relevant to task performance.

Another striking example of transient task-dependent oscillation is seen in the beta and low gamma frequency range in primate motor, premotor, and somatosensory cortex[65-69]. Short bursts of oscillation lasting from a few cycles to several seconds occur preferentially in task periods[65,66], and are more prominent in free movement and tasks requiring fine motor control compared with repetitive motor movements[65]. In tasks where the subject can prepare an action but must wait for a cue to initiate it, beta oscillations occur strongly in the delay period but are greatly reduced during movement[66,68,69], suggesting involvement in motor planning. Neuronal activity is modulated as a function of the phase of LFP oscillations, with deep modulation evident in some example units[65,67,69]. Evaluation of spike – field coherence between premotor and parietal cortex in a visually guided reaching task revealed transient oscillatory synchronisation lasting approximately 300 ms in a narrow ~15 Hz frequency band coinciding with search array onset, suggesting that bursts of beta oscillation observed in motor and premotor regions are part of larger patterns of synchronous oscillation. Consistent with this, transient bursts of beta oscillation occur in primate striatum during behaviour[70], though it is unclear whether these are coherent with cortical beta oscillations. Striatal beta oscillations were recently shown to occur simultaneously – and synchronised – with bursts of oscillation across multiple basal ganglia nuclei when rats used a cue to guide subsequent behaviour[71].

Transient bursts of oscillatory activity have a natural interpretation in an FDM framework, because by modulating activity at a frequency where it was previously unmodulated they effectively transmit the network's population code into a channel where it was not previously represented. Transient bursts of oscillation could therefore be used to selectively propagate information to those downstream networks with appropriate filtering properties[34]. Similar principles have previously been suggested to support selective communication between individual neurons using spike bursts (Box 3). Additionally, by periodically modulating excitability, oscillation bursts may affect the filtering performed by a network on its inputs. A set of connected networks engaging in a burst of coherent oscillation could therefore enhance effective connectivity amongst those participating in the oscillation relative to other inputs that do not share the modulation. Such a transient enhancement of effective connectivity between oscillating ensembles could support a proposed role of beta oscillations in stabilising the representation of selected behavioural programs[71,72].

We see changes in oscillation amplitude as fitting less neatly into a TDM framework, where the most natural way to control interactions would be to manipulate the relative phase of activity of cell ensembles. This said, a change in amplitude by definition implies a change in the distribution of spikes as a function of oscillation phase, and hence changes in amplitude could in principle play a role in systems working purely on time division principles or employing a multiplexing scheme mixing time and frequency division.

Gamma coherence in visual attention

Finally we turn to two recent studies[73,74] characterising oscillatory synchronisation between V1 and V4 during visual spatial attention tasks in macaque (Fig. 4f,g). In both tasks, two visual stimuli were presented simultaneously, located such that they were within the receptive fields of separate populations of V1 neurons but both within the larger receptive field of a population of V4 neurons. The subject was cued to pay attention to one of the two stimuli, and had to make a perceptual discrimination about the attended stimulus while ignoring the distracting stimulus. Using either iEEG[73] or LFP[74] recordings, both studies observed striking increases in synchronisation between the region of V1 representing the attended stimulus and V4, selectively in a 50 – 80 Hz gamma frequency range. The locus of attention did not substantially affect the amplitude of gamma oscillations in either V1 region, and although one study reported a slight increase in the frequency of gamma oscillations in the V1 region representing the attended stimulus[73], oscillations in both V1 regions still overlapped substantially in the frequency domain.

The oscillations in the two V1 regions were not sufficiently segregated in the frequency domain to suggest FDM; nor was there evidence of a consistent phase offset as required by TDM. We see several possible to interpretations of these findings. The coherence changes could be a signature of selective communication using spread spectrum multiplexing principles employing broadband modulation of population-coded signals in the two V1 regions. As discussed above, we think there are genuine questions about whether this could work efficiently from a signal to noise perspective, but it is the most straightforward functional interpretation of the observed coherence changes. A second possibility is that the changes in coherence play a role in controlling effective connectivity, but the multiplexing scheme used is very different from that proposed above and does not employ modulated population codes to represent information. A third possibility is that the incomplete picture of network activity currently available obscures important aspects of the network state, such as, for example, a structured rather than random phase relationship between the two V1 regions. This is suggested by observations of gamma phase reset across V1 and V4 by a ~3 Hz oscillation associated with microsaccades[75], and systematic modulation of V1 – V4 coherence with the phase of this oscillation[73]. An additional fact that may be relevant is that direct projections from V1 to V4 are sparse[76], particularly in the peripheral visual field relevant to these studies[77]. This raises the possibility that a change in oscillatory activity in an interposed area, for example an increase in gamma amplitude in a network representing only the attended stimulus, could play an important role. Finally, there remains the possibility that the observed changes in phase synchronisation could be a consequence of changes in effective connectivity implemented through some other non-oscillatory mechanisms rather than playing a functional role in controlling signal flow.

Future directions

We conclude by highlighting areas where emerging experimental techniques will help clarify the role of network oscillations in neuronal communication. The rapidly increasing size of neural ensembles that can be recorded simultaneously[78] will enable the interaction between oscillatory dynamics and population coding to be characterised in unprecedented

detail, and hence increasingly constrain how oscillations may multiplex neural signals. Of particular relevance to the multiplexing proposed here is whether modulations produced by oscillatory dynamics interact in an approximately multiplicative fashion with rate coding, and whether modulation is deep enough relative to average firing rates to achieve high signal to noise levels. Improved characterisation of how spatio-temporal structures of neural oscillation map onto convergent and divergent anatomical pathways should clarify whether and how different multiplexing principles are used to create channels for selective communication.

Moving beyond correlation, a necessary step is to evaluate the effect of manipulations of oscillatory activity on signal propagation and brain function. The use of temporally structured stimulation to either entrain on-going oscillations[79,80] or artificially induce periodic modulation at a given frequency[81] offers a powerful approach to manipulating oscillatory activity. Artificially induced oscillations may be used to test how periodic modulation of activity in a given network affects the response in target regions. Optogenetic fMRI[82] may be particularly powerful in this context as the haemodynamic response can be evaluated in parallel across many target regions, potentially revealing differences in filtering properties of different projections from a given network. Entrainment of on-going oscillatory activity in behaving animals or human subjects offers the possibility of directly manipulating inter-regional synchronisation or the relative phase of oscillation to determine effects on function. A pioneering recent study manipulated theta oscillations during a visual working memory task using dual site transcranial alternating current stimulation over frontal and parietal cortex[83]. In-phase stimulation significantly reduced reaction times while anti-phase stimulation increased them, providing evidence for a causal role of theta band synchronisation in communication between these areas.

Through detailed characterisation and targeted perturbation of oscillatory activity, we expect rapid progress in identifying the coding principles and algorithmic operations through which oscillatory network dynamics influence neuronal communication.

Acknowledgements

Glossary

Effective connectivity	Following ref. [84] we use the term effective connectivity to describe 'the influence one neural system exerts over another'.
Local field potential	The voltage signal recorded from extracellular space in neural tissue. The lower frequency components (<250 Hz) are thought primarily to reflect synaptic activity within a few hundred micrometres of the electrode[85].
Amplitude	A measure of how much a periodic signal varies over the course of its cycle. Amplitude can be quantified in various ways including peak-to-

peak amplitude – the difference between the highest and lowest value reached by the signal during the cycle.

Integrate and fire neuron	Simplified neuron models used widely in network simulations in which the biophysical processes generating the action potential are not explicitly represented. Instead, the neuron is said to have spiked whenever the membrane potential crosses a threshold value.
Poisson neuron	A stochastic neuron model in which the spike train is generated by a Poisson process, with spike probability specified entirely by the firing rate, which is in general a function of time.
Aliasing	When a signal is sampled at a rate that is too slow to capture its variation, the contribution of high frequency components to the sampled values is ambiguous, leading to noise when the signal is reconstructed from the samples.
Coherence	A statistic used to evaluate the similarity of two signals as a function of frequency. Coherence at a given frequency is affected by both the covariance of the amplitude and the consistency of the phase relationship between the signals at that frequency. The absolute value of coherence measures involving spike trains strongly depends on the firing rate of the units used in the analysis[86-88]. This dependence complicates relating such measures to underlying variables of interest such as the consistency of phase relationship between oscillations in two regions. Alternative measures of phase synchronisation have recently been developed which overcome many of the limitations of coherence when applied to spike trains[88].

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Box 1

Network Oscillations

Network oscillations are states in which the activity of a population of neurons is periodically synchronised, i.e. in which the spike probability of individual neurons exhibit periodic auto- and cross- correlations. Network oscillations have been an active area of research since Hans Berger's seminal 1929 observation of oscillations in the electrical potential of the scalp over occipital cortex in human subjects with their eyes closed. He termed this large amplitude ~10 Hz activity 'alpha' oscillations, and distinguished it from higher frequency, smaller amplitude 'beta' oscillations observed when subjects opened their eyes. This nomenclature for classifying neural oscillations by their frequency survives to this day and has been expanded to include delta (1 – 4 Hz), theta (4 – 10 Hz), beta (10 – 30) and gamma (30 – 80 Hz) bands. Network oscillations have emerged as a major field of research in contemporary neuroscience as it has become clear that periodic synchronisation is a prominent feature of both spontaneous brain activity and that evoked by sensory stimulation, and that changing patterns of network oscillation are often tightly correlated with behaviour or features of sensory stimuli.

Oscillatory synchronisation of neurons can arise through diverse mechanisms, recently reviewed in ref [2]. One important distinction is between *spike-to-spike* synchrony and *sparsely synchronised* oscillation[2,3]. In spike-to-spike synchronous states individual neurons spike regularly, and are brought into synchrony via chemical and/or electrical synapses. Whether coupled neurons synchronise in this way depends on how activity of each neuron affects the phase of other neurons it is coupled to. This can be characterised by their phase response curves (PRCs), which in turn depend on their synaptic and intrinsic neuronal properties. Any synchronising effect of the synaptic coupling must overcome differences in the intrinsic spiking frequency of the individual neurons and the desynchronising effects of noise.

By contrast, in sparsely synchronised states individual neurons spike irregularly, but the oscillation emerges in the aggregate firing rate of the entire neuronal population. Oscillatory dynamics at the network level occur as a result of delayed negative feedback, which can arise either through self-inhibition of an exclusively inhibitory neuronal population, or through reciprocal innervation of excitatory and inhibitory sub-populations[3]. This mechanism can be understood by considering the effect of a random fluctuation in excitatory drive, which transiently raises firing rates. In a network with strong delayed negative feedback this will lead to a subsequent undershoot in firing rates below equilibrium. This will in turn lead to an overshoot of firing because of disinhibition, leading to a population oscillation. Depending on the strength and delay of the negative feedback, these dynamics can give rise either to a self-sustaining oscillation, or resonance at a particular frequency[34,35]. The firing rate of neurons participating in sparsely synchronised oscillations can be highly heterogeneous allowing firing rate population coding to coexist with oscillatory activity.

Box 2

Orthogonality

Two functions $f(t)$ and $g(t)$ are orthogonal over the interval $a \leq t \leq b$ if their overlap integral is zero, i.e. if they satisfy the following equation:

$$\int_a^b f(t)\, g(t)\, dt = 0$$

We suggest that orthogonality plays an important role in the hypothesis that effective connectivity between two regions can be selectively enhanced by modulating neuronal gain in one region coherent with modulation of firing rates in the other region. The simplest model of gain modulation is to treat a change in gain as a change in the slope of a linear input – output function. In such a model, the effect of a temporal pattern of gain modulation $g(t)$ on the average gain for an input with firing rate modulation $f(t)$ is given by the overlap integral of f and g. To selectively enhance the average gain for a 'target' input relative to that for other distracting inputs, a receiving network must therefore generate a pattern of gain modulation that has a large overlap with the modulation of the target input but is as close as possible to orthogonal to those of the distracting inputs. This is straightforward where different inputs are segregated in time or frequency as illustrated in Fig. 2, but not for inputs oscillating incoherently in the same frequency band.

Box 3

Multiplexing in single spike trains

Spike bursts in individual neurons have been proposed to support selective communication between individual neurons by interacting with subthreshold resonances[22,89], such that a burst at a given frequency elicits spikes only in those downstream neurons with an appropriate resonance frequency. This form of multiplexing is conceptually similar to FDM of population codes discussed in the main text as in both cases the amplitude of fluctuation in a spike train at given frequency acts as a channel for communication, the key difference being whether it is the spike train of a single neuron or of a population that is modulated. Selective communication by bursts and sub-threshold resonance is an example of amplitude to firing rate conversion implemented through bandpass filtering by sub-threshold resonance followed by rectification by the spike threshold. Multiplexing at the scale of individual neuron spike trains and population activity patterns are not mutually exclusive. However, selective communication by bursts is presumably restricted to regimes in which the strength of individual synapses is large enough, and background synaptic input low enough, that a burst in a single neuron produces a change in the frequency content of the input to downstream neurons detectable above noise from background synaptic activity.
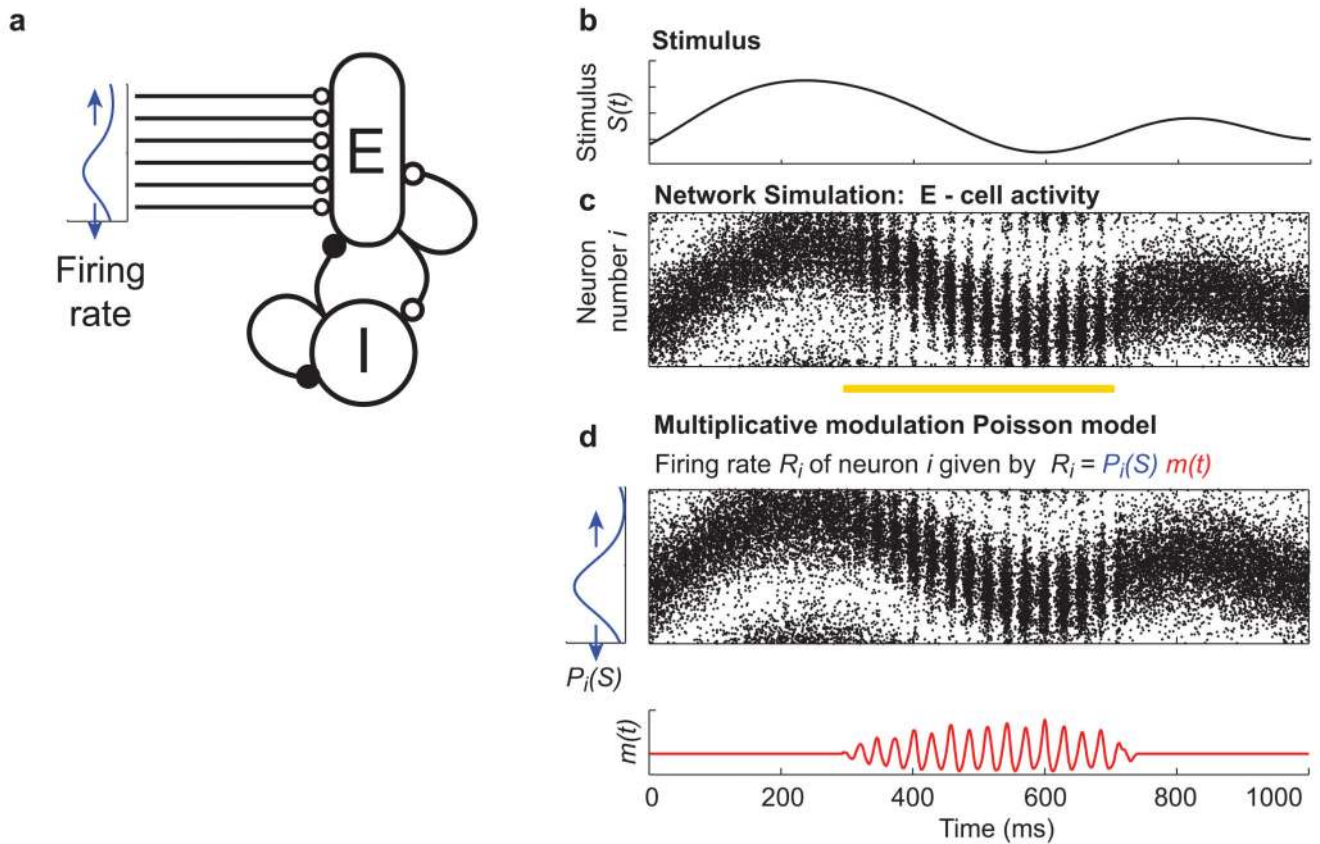
Figure 1. Multiplicative modulation from oscillatory dynamics
(a) Schematic illustrating a network model consisting of an excitatory (E) and an inhibitory (I) population of integrate and fire neurons, recurrently and reciprocally connected. A time varying stimulus **(b)** is encoded by the activity of the excitatory population as a firing rate population code with bell shaped tuning curves, such that as the value of the stimulus changes a localised bump of activity moves across the population **(c)**. The stimulus tuning is inherited from spatially patterned external input, i.e. the firing rate of external input received by excitatory cells varies across the population as a bell shaped curve (**a** – blue trace), the position of which changes with the value of the stimulus (**a** - blue arrows). The network transitions from an asynchronous to a sparsely synchronised state[3] (Box 1) and back again as a result of a change in recurrent synaptic connection strengths, which could occur for example due to altered neuromodulation (yellow bar indicates period with modified synaptic weights). The network oscillation produces an approximately multiplicative modulation of the firing rate population code. This can be seen from the close similarity of the simulated activity in (**c**) to that of a population of Poisson neurons (units with uncorrelated inter-spike intervals whose firing probability is determined entirely by a time varying instantaneous firing rate) shown in (**d**). The firing probability of each unit was generated by a bell-shaped spatial pattern of activity (blue curve), whose position varied with the stimulus, multiplicatively modulated by a rapidly oscillating 'carrier' signal during the oscillating state (red curve). Network model is the input network from ref [34].

Demultiplexing by coherent gain modulation:

a   Time division
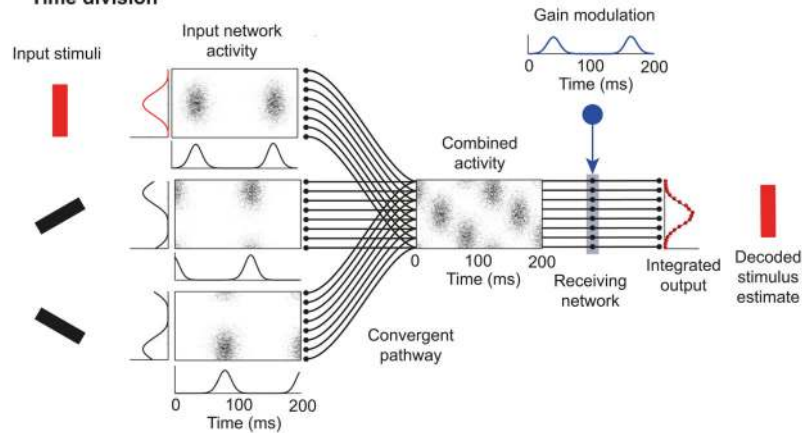
b   Frequency division
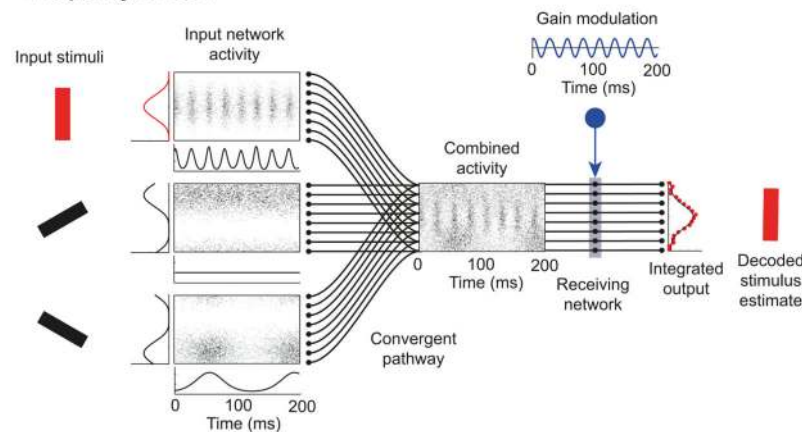
c   Demultiplexing by amplitude to firing rate conversion.
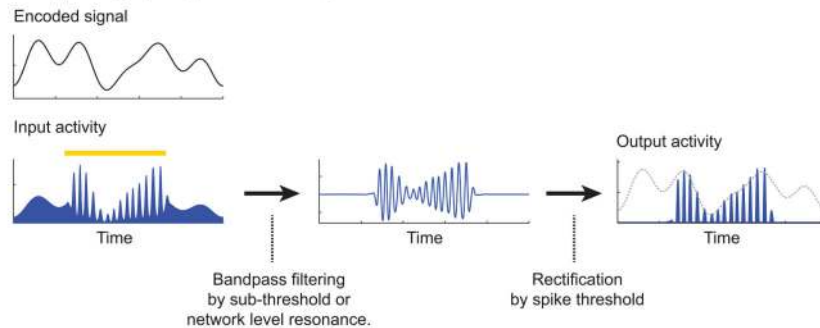
Figure 2. Selective communication using time and frequency division multiplexing
(a, b) Schematic showing how selective communication can be achieved through coherence between oscillations in a sending (input) network and periodic gain modulation in a receiving region. A set of three input networks encode separate stimuli, in this case the orientation of a bar, as a firing rate population code. Each input network consists of a population of Poisson neurons whose firing rate is given by a bell shaped tuning curve with respect to stimulus orientation, multiplied by an oscillatory modulation that is common to all neurons in a given input network (as in figure 1d). For each input network we show the

spatio-temporal pattern of activity over 200 ms (box), the average firing rate of each neuron (curve left of box), and the oscillatory modulation (curve below box). These input networks converge to provide a combined input to a receiving network. The information encoded in one input network (the 'target' input shown in red), can be selectively routed through the convergent pathway by periodic modulation of the gain of neurons in the receiving network coherent with the oscillation of the target input (gain modulation input is shown in blue, the time course of gain modulation shown by the blue trace). The receiving network was not modelled biophysically but rather consisted of units with a linear input – output function whose slope was determined by the gain modulation input. The output of the receiving network is integrated over time to produce a spatial pattern of activity that reflects only the activity of the target input, from which the target stimulus can be accurately estimated. In panel (a) time division principles are used to segregate the activity of the different input pathways; each input is modulated at a different phase relative to a single oscillation. In panel (b) frequency division is used to segregate the different inputs; one distracting input oscillates in a frequency band that does not overlap with the target input, while the other distracting input is asynchronous and hence only transmits its population code into the average firing rate or 0 Hz channel. Note that the gain modulation in the receiving network takes both positive and negative values. Positive and negative net gain can be implemented by an excitatory pathway balanced by feed-forward inhibition. Adapted from ref [26]. **(c)** An alternative method to achieve selective readout of frequency-division multiplexed signals. A time varying signal ('encoded signal' on figure) is encoded into the firing rate of an input population. Input activity is multiplicatively modulated during a transient burst of oscillatory activity (indicated by yellow bar), reproducing the encoded signal into the amplitude envelope of firing rate fluctuations at the oscillation frequency. By bandpass-filtering and then rectifying the input activity, the encoded signal can be selectively recovered when the input activity is modulated at the appropriate frequency but otherwise ignored, allowing bursts of oscillatory activity to propagate information selectively. A biophysical model implementing selective communication using this principle is detailed in ref [34].
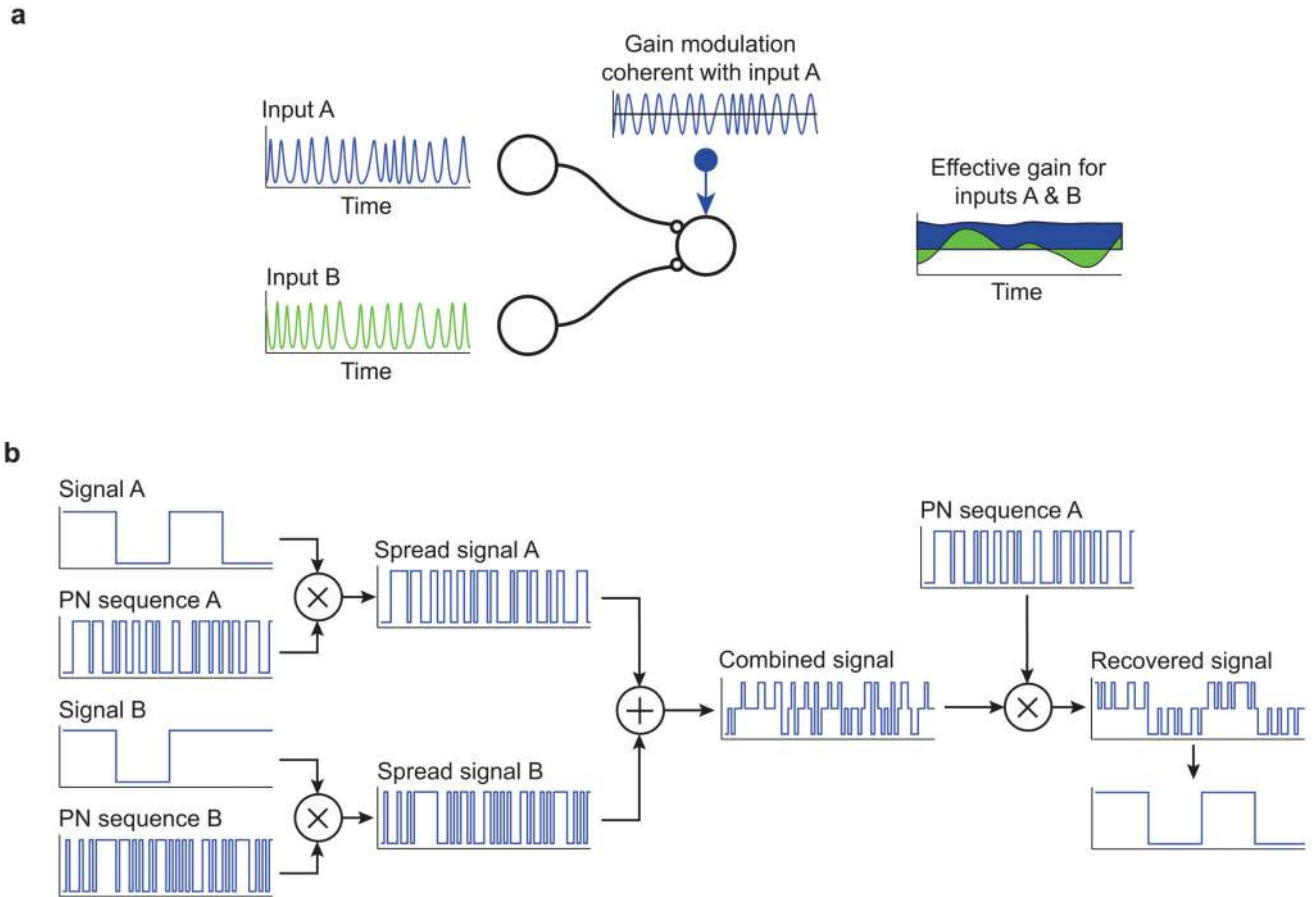
Figure 3. Communication through coherence (CTC) as spread spectrum multiplexing
(a) Two networks, A & B, oscillating incoherently in the same broad frequency band
provide convergent input to a receiving network. Applying gain modulation to units in the
receiving network coherent with input A can increase the average gain for that input relative
to input B. However, this is achieved at the cost of fluctuations in effective gain for input B
as it drifts in and out of phase with A (effective gain plotted in the right panel is the overlap
of each input's oscillation with the gain modulation waveform, smoothed with a Gaussian of
standard deviation one oscillation period). These fluctuations act as a source of noise and
degrade the accuracy of selective communication when compared with situations where
different inputs are segregated by time- or frequency- division principles. **(B)** Code division
multiple access (CDMA), a spread spectrum multiplexing scheme used in
telecommunication, provides a useful analogy with multiplexing in the CTC hypothesis.
Two digital signals, A and B, are modulated by different binary pseudorandom noise (PN)
sequences known as spreading codes. The rate of the PN sequence is much higher than the
rate of the signal; in this example each bit of the signal corresponds to 16 bits of the PN
sequence. Modulation can be achieved simply by multiplying the signal with the PN code if
true and false binary values are treated as 1 and −1 respectively. The resulting spread signals
are combined for transmission through a single physical communication channel. For clarity
we show simply the sum of the digital spread signals, though in practical applications the
digital signals are typically encoded into modulation of an analogue carrier wave. A receiver

can selectively recover one of the component signals by correlating the combined signal with the appropriate PN sequence.
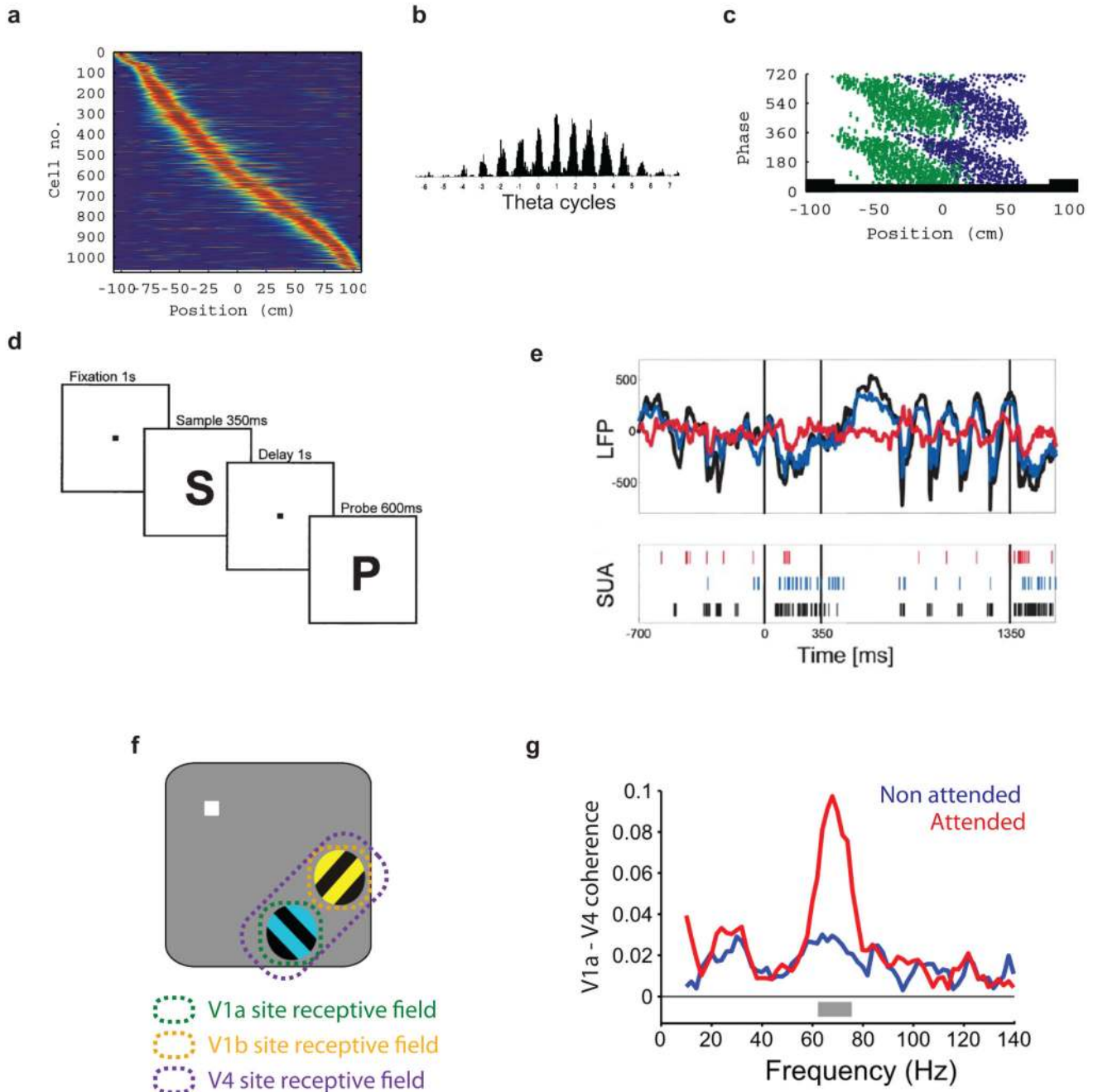
Figure 4. Network oscillations in behavioural tasks

(a – c) Activity during theta oscillations in rodent hippocampus appears consistent with time division multiplexing of firing rate population codes. Data shown is from recordings in the CA1 region during runs in a single direction on a linear track. **(a)** Normalised firing rates of ~1,000 neurons as a function of the animal's position, sorted along the Y-axis by the position of peak firing. The firing rate of individual cells is tightly tuned for the animal's position on the track and the distribution of firing rates across the population of cells forms a population code for position. **(b)** Spike count for a single cell as a function of theta phase

constructed from multiple runs through the cell's place field. Spikes were aligned by theta phase and number of theta cycle relative to the time at which the rat passed a given position near the centre of the place field. Note the slow change in average firing rate relative to the rapid oscillatory modulation consistent with a separation of timescales between variation of the encoded variable and the oscillatory modulation. Note also the strong correlation across cycles between average firing rate and amplitude of firing rate modulation, consistent with approximately multiplicative modulation of activity by the network oscillation. **(c)** Activity of two cells as a function of position and theta phase. The two cells are active at largely non-overlapping phases of theta, as required for time division multiplexing, and both precess to earlier phases as the animal traverses the place field. **(d - e)** Bursts of network oscillation are a possible signature of selective communication using frequency division principles (see main text). One striking example of an oscillation occurring at a specific point during behaviour has been reported in area V4 in a working memory task in macaque. **(d)** Sequence of events during each trial of the task; after visual fixation on a central target, monkeys were presented with a sample stimulus followed, after a delay period, by a probe stimulus. If the probe stimulus was the same as the sample, the subject could obtain a reward by releasing a lever, while if the probe differed from the sample, reward was obtained by withholding the response. **(e)** Local field potential recordings in visual area V4 showed theta frequency oscillation selectively during the delay period (top panel). Simultaneously recorded spike activity in V4 showed phase locking to the delay period theta oscillations (bottom panel). **(f, g)** Striking changes in gamma band coherence have recently been reported between V1 and V4 in visual attention tasks. **(f)** Two drifting gratings were presented in the peripheral visual field while a monkey fixated on a central spot. The stimuli were spaced such that each was represented by separate V1 regions but both fell within the receptive field of a single V4 region. Activity in all three regions was simultaneously monitored using ECoG. The fixation target changed colour to indicate which grating should be attended on a given trial. The subject had to detect a subtle change in the shape of the attended target while ignoring any change in the distracting stimulus. **(g)** Though both attended and unattended target induced oscillations of comparable amplitude in a 50 – 80 Hz gamma band in their respective V1 regions (not shown), coherence was dramatically enhanced between the region of V1 representing the attended stimulus and V4. These findings have been interpreted in the CTC framework as a mechanism for selectively routing information from the attended V1 region to V4. The observations appear inconsistent with either time- or frequency- division multiplexing as the oscillations in the two V1 regions overlap substantially in frequency and do not have a consistent phase offset. See main text for further discussion. Adapted from references; **a,c** [49], **b** [42], **d,e** [63], **f,g** [73].