Communication between Brain Areas Based on Nested Oscillations

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Abstract

Unraveling how brain regions communicate is crucial for understanding how the brain processes external and internal information. Neuronal oscillations within and across brain regions have been proposed to play a crucial role in this process. Two main hypotheses have been suggested for routing of information based on oscillations, namely the 'communication through coherence' and the 'gating by inhibition' frameworks. Here, we propose a framework unifying these two hypotheses that is based on recent empirical findings. We discuss a theory in which communication between two regions is established by phase-synchronization of oscillations at lower frequencies (<25Hz), which serve as temporal reference frame for information carried by high frequency activity (>40Hz). Our framework, consistent with numerous recent empirical findings, posits that cross-frequency interactions are essential for understanding how large-scale cognitive and perceptual networks operate.

Significance statement

To understand how the brain operates as a network it is essential to identify the mechanisms supporting communication between brain regions. Based on recent empirical findings, we propose a novel mechanism for selective routing based on cross-frequency coupling between slow oscillations in the alpha and gamma band.

Main text

Humans operate in complex environments requiring the encoding and processing of the constant flow of sensory information. While the information must be prioritized, the mechanisms underlying the selective routing of sensory information remain to be understood. Neuronal oscillations, in which excitability is modulated by the phase of the rhythm, have been proposed to play important mechanistic roles for routing information, since they can change the dynamic interactions between brain regions on a fast time scale (Varela, et al. 2001). Two hypotheses have been proposed for routing of information based on oscillations: the 'communication through coherence' (CTC; Bastos, et al. 2015, Fries 2005, 2009) and the 'gating by inhibition' (GBI; Jensen and Mazaheri 2010) frameworks (see also Akam and Kullmann 2014). The CTC framework, at least in its initial form, mainly focused on gamma activity (>30Hz) while the GBI

is mainly based on alpha oscillations (8-13Hz). These two frameworks are not mutually exclusive and the aim of this paper is to unify them.

The CTC and GBI frameworks

Consider two pools of neurons A and B that are connected to a third pool C. As an example, this could be two subpopulations of neurons representing different spatial locations within V1 and project to a common subpopulation of V4 neurons that represent both spatial locations. When spatial attention is directed to the receptive fields (RFs) of neurons in pool A, the routing mechanism should favor the communication between A and C while preventing the communication between B and C (figure 1a). How is the functional connectivity between A and C, but not B and C, established?

According to the CTC hypothesis, inter-regional communication is established when the oscillatory activity between these neuronal pools is coherent, i.e. they oscillate at the same frequency with a stable phase difference (Fries 2005, 2009). This would allow the excitable phase of neurons in C to coincide with synaptic input from neurons in A. To block the communication (the B to C pathway), the synaptic input from neurons in B arrives at the non-excited phase of the neuron in C (figure 1b). Thus if B and C are not oscillating in phase-synchrony the communication is reduced. Brain regions have indeed been shown to phase-synchronize in the gamma band when attention is allocated (e.g. Bosman, et al. 2012, Womelsdorf, et al. 2006, Womelsdorf, et al. 2007). How is the phase-synchrony between regions A and C established? Fries and colleagues (Bastos, et al. 2015, Fries 2009) proposed that it is established by oscillations in neurons of pool A entraining neurons in C at the gamma frequency. This mechanism also implies that the phase-synchronization among the neurons in A is stronger and potentially oscillates at a faster gamma frequency than in B (Fries 2015). As a consequence, the neurons in C are entrained by A rather than B, thus dynamically strengthening the functional connectivity. This effect results in a mechanism that increases the impact of A on C while reducing the impact of B on C (Fries 2009, 2015). It is not completely clear how B and C achieve asynchrony (Akam and Kullmann 2014). As demonstrated in Bosman et al. (Bosman, et al. 2012), coherence between B and C is reduced as compared to coherence between A and C. The reduced coherence could be achieved by B and C fluctuating independently in the same frequency band, or by B and C oscillating at different frequencies (as shown in Bosman, et al.

2012). Yet, a possibility is that they oscillate at the same frequency but with a fixed phase difference (e.g. anti-phase); however, this possibility seems at odds with the reduced coherence in the unattended pathway (Bosman, et al. 2012).

According to the GBI hypothesis (figure 1c), the information flow between regions is established by actively inhibiting the pathway not required for the task. It has been proposed that alpha activity reflects regional-specific inhibition (Foxe and Snyder 2011, Jensen and Mazaheri 2010, Jensen, et al. 2012, Klimesch, et al. 2007). Alpha activity is associated with pulses of inhibition, i.e. the larger the alpha activity, the stronger the bouts of inhibition. This is consistent with findings from many experiments showing that alpha activity is high over task-irrelevant areas (Bonnefond and Jensen 2012, Capilla, et al. 2014, Haegens, et al. 2010, Snyder and Foxe 2010 but see Mo, et al. 2011) or task-irrelevant groups of neurons within a brain area (van Kerkoerle, et al. 2014). Furthermore, this increase has been shown to predict behavioral performance (Bonnefond and Jensen 2012, Bonnefond and Jensen 2013, Foxe, et al. 1998, Haegens, et al. 2011, Haegens, et al. 2012, Handel, et al. 2011, Meeuwissen, et al. 2010, Myers, et al. 2014, Payne, et al. 2013, Thut, et al. 2006). Considering Figure 1a, gating would thus be reflected by alpha power increases in B and a decrease of alpha power in A and C. Furthermore, the alpha power decrease in A and C would allow for increased gamma power in these regions that could be involved in transmitting information. It is important to note that, in the latest version of the CTC framework (Fries 2015), Fries also highlighted the potential role of alpha oscillations, in opposition to gamma oscillations, in preventing effective communication of local neuronal representations but also in holding these representations "on-stock" so they can be flexibly used when needed.

Even though both of these frameworks have strong explanatory value, they account for different findings in the literature. In particular, CTC in its current formulation does not address the issue of diverging routes where e.g. one region is connected to two downstream regions. In this case the entrainment by gamma oscillations does not provide a routing mechanism (but see Bastos, et al. 2015, Fries 2015). Several other challenges have been put forward to the CTC framework. One criticism is based on the finding that the gamma frequency is modulated by stimulus features such as contrast (Hadjipapas, et al. 2015, Ray and Maunsell 2010). This implies that different contrast levels that are part of a larger scene (e.g. a single object) are communicated at different frequencies, which might pose a problem for integrating this

information in the converging visual hierarchy (Ray and Maunsell 2010). However, Fries (2015) mentioned that the stimulus salience and level of attention to the subparts of a single object are often similar and thus result in similar gamma frequencies facilitating the integration in higher levels of hierarchy. However, a second criticism is based on an optogenic study that manipulated spike timing in the gamma and beta bands. Manipulating the temporal coordination of spiking activity did not influence behavior or transmission of spikes (Histed and Maunsell 2014). Third, there is a debate as to whether the high frequency activity generated by natural stimuli is dominated by band-limited oscillations in the gamma frequency range or non-oscillatory changes over a broad range of frequencies (Hermes, et al. 2014; see section "Existing evidence and predictions for communication by nested oscillations"). Finally, it has been argued based on results from a modeling study, that while entrainment might occur, communication is established already prior to coherence (Rolls, et al. 2012).

Also the GTI framework is associated with several limitations. First, the phase modulation of neuronal firing by the alpha band activity is not made explicit (Jensen, et al. 2012, Jensen, et al. 2014). Second, GTI does not elaborate on the role of gamma band activity for inter-areal communication nor does it consider interregional phase-synchrony in the alpha-band as also being involved in inter-regional communication. Third, the strong emphasis on the alpha band activity seems at odds with many non-human primate studies on attention in which modulations by alpha oscillations have only been recently reported, mainly via the use of laminar recordings (Haegens, et al. 2011, Haegens, et al. 2015, Maier, et al. 2011, Spaak, et al. 2012).

At different levels of the cortical hierarchy feedforward and feedback information needs be integrated (see e.g. Larkum 2013 for one proposal). The GTI and CTC proposals are not fully explicit on the integration of feedforward and feedback at the microcircuit level (but see Lee, et al. 2013 cited in Bastos, et al. 2015 and Fries 2015). Therefore it is crucial that these frameworks are unified and extended (e.g. by incorporating the phase coding scheme), so that empirical studies can be specifically designed to test for the predictions derived from such a unified framework.
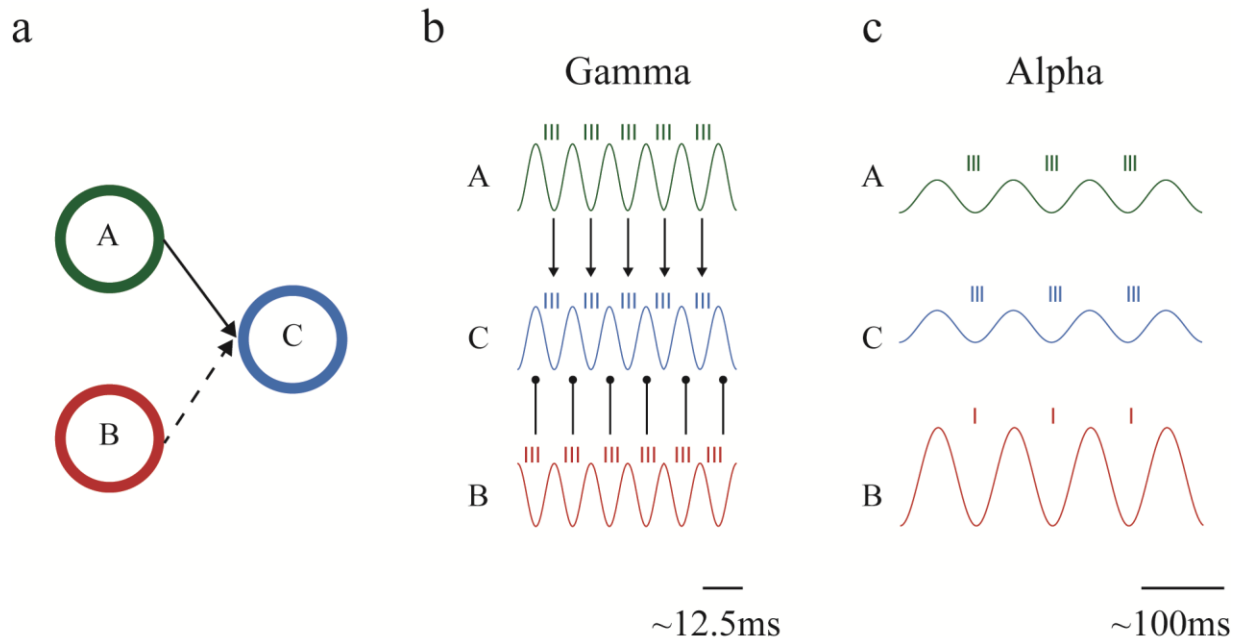
Figure 1: The communication-through coherence (CTC) and gating through inhibition (GTI) hypotheses. **a.** Two pools of neurons (A and B; e.g. in V1) are connected to a pool of neurons (C; e.g. V4). In this example, pool A communicates with C (solid line) while functional connectivity between B and C is suppressed (dashed line). **b.** Communiction through coherence (CTC). The waveforms represent oscillatory population activity (as measured in the LFP) in the three regions whereas the small vertical lines represent spiking activity. The phase of the oscillatory activity modulates the excitability and thus spike timing, i.e. it is the phase relationship between the regions determining the routing. The neurons in A and C oscillate in phase, whereas the neurons in B do not oscillate in phase with C. It has been proposed that this mechanism is implemented by gamma band oscillations (>30Hz) (Fries 2005) **c.** Gating by inhibition (GBI): The flow of information is controlled by an increase of alpha-band oscillations (~10Hz) which inhibits firing in pool B, and a decrease in alpha oscillations of neurons in A and C allowing communication by release from inhibition (Jensen and Mazaheri 2010). It is the magnitude of the pulses of inhibtion and thus the alpha power that controls the routing.

A unified framework based on nested oscillations

We here propose a unified framework which is based on the coupling of slow and fast oscillations (see also Florin and Baillet 2015, Hyafil, et al. 2015, Lakatos, et al. 2005, Schroeder and Lakatos 2009). In this framework (figure 2), we suggest that the information flow is established by neuronal synchronization at lower-frequencies in the theta ($4-7$Hz), alpha ($8-13$ Hz) and beta ($14-25$Hz) bands rather than in the gamma band. We will first develop the framework around the alpha band in the visual system (see section "Communication based on nested oscillations could be a general mechanism throughout the brain" for a discussion about the role of beta oscillations in the visual system). This is motivated by the fact that there are a numerous empirical reports on alpha oscillations in the visual system in the context of experiments in which routing is manipulated using attention task. We will then discuss how the framework could generalize to other regions.

We consider here that alpha oscillations are associated with pulses of inhibition every ~100 ms and as such can suppress neuronal activity locally as well as support inter-areal communication, through phase-synchronization and release of inhibition (see also section on Control of alpha oscillations in relation to cortical layers). It is important to note that these mechanisms do not exclude complementary roles of alpha oscillations in other processes such as transmitting prior-evidence to sensory areas (Sherman, et al. 2016) or sampling (Busch and VanRullen 2010, Song, et al. 2014, VanRullen 2016; see also section "The role of saccades and slower rythms").

We propose that, when neurons in pool A and C communicate, they oscillate coherently in the alpha band in conjunction with a decrease in alpha power. The decrease in alpha power creates longer windows of excitability in each cycle, i.e. longer duty-cycles (Jensen and Mazaheri 2010), allowing for more information to be transferred between the synchronized regions. The blocking of communication between pool B and C is assured by two complementary mechanisms: asynchrony between B and C preventing communication and stronger alpha power in B resulting in shorter duty-cycles. Asynchrony could mean that the regions are oscillating in anti-synchrony which could imply that they are still coherent. Another possibility is that they are not synchronized, but fluctuating at different phases albeit the frequencies are within the same range. Another possibility would be that pools B and C fluctuate at different frequencies. In the latter case, the prevention of the transfer of information would be mainly implemented via an increase of alpha inhibition.

Gamma oscillations are expected to be nested within alpha oscillations, i.e. they should occur only during the excitability phase of alpha oscillations. In pool A, the low magnitude of alpha oscillations allows for longer duty cycles, i.e. longer time-windows for the gamma activity during the excitability phase of the alpha cycle. As the excitable phase of the alpha oscillations will be aligned between the two relevant pools of neurons, gamma activity in A will be able to impact the neurons in C. This fast neuronal synchronization will have a strong impact on C due to synaptic summation within the time window of a gamma cycle (Salinas and Sejnowski 2001).
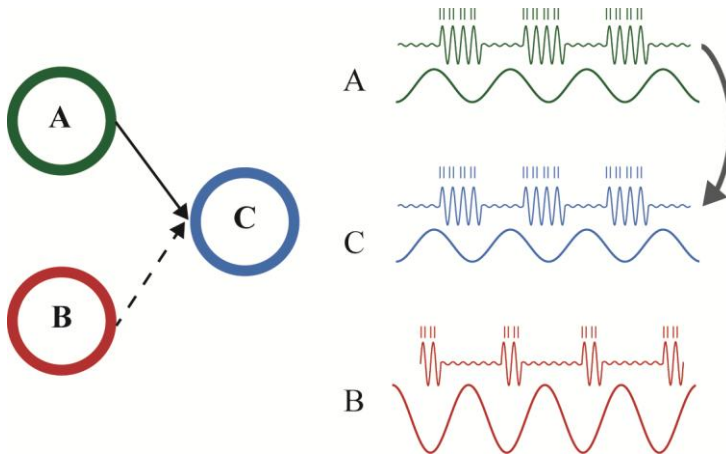
Figure 2: The new framework. The synchronization in the alpha-band establishes the functional connection between A and C. This allows for representational specific neuronal firing reflected by the gamma band activity to flow to region C. The blocking of communication between B and C is achieved by high alpha power in B and an asynchrony between B and C. Therefore both modulations in alpha-band power, as in gating by inhibition, and phase-synchronization between the regions, as in CTC, are determining the routing of information between regions. Note that phase-synchronization is assumed in the alpha band and the information transfer is reflect by gamma band activity.

As a consequence, gamma oscillations in A and C will be correlated and possibly coherent. In pool B, the high magnitude of alpha oscillations will reduce the duty cycle, i.e. the gamma oscillations duration. In addition, the asynchrony of alpha oscillations in B and C will prevent gamma activity in B to drive cells in C. In short, a coupling between the phase of the alpha oscillations and gamma power could reflect the temporal coordination of information between regions.

The significance of alpha synchronization, specifically in a sensori-fronto-parietal network, in sensory processing was also emphasized by Palva and Palva (2007, 2011) and more recently in Siebenhühner et al. (2016). They proposed that cross-frequency phase coupling between alpha, beta and gamma oscillations would allow the selection and maintenance of object representations during perception and working memory. They more specifically proposed that cross-frequency phase synchrony between the fronto-parietal network and the local gamma oscillations in sensory regions might underlie the incorporation of stimulus representations into the focus of attention. The current framework shares many similarities with their inspiring framework. The framework developed here is, however, very specific on how the modulation of 1) the local amplitude of alpha oscillations 2) the inter-areal phase-alignment and 3) how the local interaction between the phase alpha oscillations and the power (not the phase) of feed-forward gamma oscillations is involved in the selective routing of information in cognitive

networks. Furthermore, the current framework incorporates the phase coding scheme and discusses the implementation of the model within the cortical layers. Finally, we attempt to generalize the model by considering that other slow rhythms could implement the specific inter-areal communication in other networks.

Existing evidence and predictions for communication by nested oscillations

Testing the proposed framework would require recordings from different regions in humans or non-human primates in the context of a task as for instance done by Saalmann et al. (2012). In this study, monkeys were cued to covertly attend to one of six locations after which a target array appeared. In the delay between cue and target, the allocation of covert attention was associated with an increase in coherence between V4 and temporo-occipital areas. Moreover, gamma coherence between V4 and TEO phase-locked to the alpha oscillations was observed. These results support our framework by demonstrating that alpha-band coherence is in control of the communication. While these findings provide first support for our framework, we will outline set of more specific predictions applied to the visual system in the following:

Prediction 1: Alpha oscillations are a consequence of internal control while gamma activity reflects feedforward communication. Moreover, gamma activity is phase-locked to the alpha oscillations.

The framework predicts that alpha oscillations set up the communication between relevant areas in a given task context. This idea implies that the phase and power of the alpha oscillations are under internal control. The gamma oscillations phase-modulated by the alpha oscillations will then reflect the information to be transferred in a feedforward manner.

Several recent papers have provided evidence in favor of slow frequency activity (alpha and beta oscillations) reflecting feedback control and gamma activity reflecting feedforward processing within the visual hierarchy (Bastos, et al. 2015, Jensen, et al. 2015, Michalareas, et al. 2016, van Kerkoerle, et al. 2014, von Stein, et al. 2000, see also Arnal, et al. 2011). Using granger causality measures, they showed that alpha/beta oscillations in higher-order visual regions impacted lower-order regions during an attention task while the reverse was observed for gamma oscillations. Van Kerkoerle et al. (van Kerkoerle, et al. 2014) further demonstrated that electrical stimulation of V1 induced an increase of gamma activity in V4 while stimulating V4

induced an increase of alpha oscillations in V1. The prediction regarding the control of alpha oscillations goes beyond feedback control and we elaborate on many possibilities on where alpha is generated in the section "Control of alpha oscillations in relation to cortical layers". It is important to note that gamma oscillations also can reflect feedback communication (Bastos, et al. 2015, Michalareas, et al. 2016; possibly controlled by alpha oscillations).

It has recently been shown that alpha and gamma activity interacts: gamma activity is phase-coupled to alpha oscillations during rest and during stimulus anticipation and processing in both monkeys and humans (Berman, et al. 2014, Bonnefond and Jensen 2015, Florin and Baillet 2015, Khan, et al. 2013, Spaak, et al. 2012, 2012, Voytek, et al. 2010). Two studies have demonstrated that the higher the alpha activity, the lower the gamma activity at a specific phase of alpha oscillations during rest in monkeys and during the retention period of a working memory task in humans. This is in line with alpha activity being associated with pulses of inhibition every ~100ms (Bonnefond and Jensen 2015, Spaak, et al. 2012). We propose that gamma oscillations, nested within slow-oscillations serve to segment the neuronal representations in time. According to this framework a neuronal representation is constituted by a distributed firing pattern constrained to a given gamma cycle (Lisman and Idiart 1995). This allows for several items to be multiplexed over a gamma cycle (see section "Exchange of phase encoded information").

However, there is currently a debate to whether gamma activity reflects oscillations or whether they are a broad-band phenomenon devoid of rhythmicity, in particular for >80Hz oscillations (Brunet, et al. 2014, Buzsaki and Schomburg 2015, Hermes, et al. 2014, Lachaux, et al. 2005, Ray and Maunsell 2015). The broad-band activity (often called high-gamma activity or even epsilon when > 80Hz) is likely to reflect a hash of neuronal spiking rather than oscillations. However, it is possible that the 30-150 Hz activity is composed of both true oscillatory gamma activity (Brunet, et al. 2014) and broad-band multi-unit activity (Manning, et al. 2009, Ray and Maunsell 2011). Possibly, the 80-150Hz activity reflects the firing of neural populations, which is phase-locked to gamma oscillations at lower frequencies (30-80Hz), as has been observed in the rat hippocampus (Belluscio, et al. 2012).

This is an important issue as the CTC framework articulates a mechanistic role for the phase of gamma oscillations such that the information can be transferred via inter-areal

synchrony. The nature of activities observed in different gamma frequencies needs therefore to be further investigated using intracranial animal or human data.

In the present framework, the neuronal representation could contain both rhythmical activity (cf e.g. section "Exchange of phase encoded information") or broad-band activity devoid of rhythmicity as the selectivity of the communication is subserved by an inter-areal synchronization at lower frequencies, i.e. theta, alpha or beta.

Moreover, as pointed out above the modulation of gamma frequency by different visual features (e.g contrast) is difficult to reconcile with the CTC framework. This would result in different parts of an object being communicated at different frequencies in the visual hierarchy preventing integration (but see Fries 2015). In the present framework, the gamma activity generated by the different features of a stimulus would be represented at different phases of a single alpha cycle in a multiplexing manner which then allows for integration. In future work, it will be interesting to investigate whether alpha oscillations indeed serve to group and integrate sensory input.

Prediction 2: Alpha magnitude and inter-areal synchrony controls the transfer of information carried by gamma oscillations.

The framework assumes that alpha band phase-synchrony between A and C (see figure 2) allows stimulus-driven gamma oscillations, modulated by the phase of the alpha oscillations, to be transferred from A to C. Specifically we hypothesize that the synchrony of alpha oscillations between relevant areas predicts inter-areal correlation or coherence of gamma oscillations.

While the inter-areal coherence observed in the alpha and gamma band during several cognitive processes in rats, monkeys and humans (Bastos, et al. 2015, Bosman, et al. 2012, Grothe, et al. 2012, Muller and Weisz 2012, Pollok, et al. 2007, Popov, et al. 2013, van Kerkoerle, et al. 2014, Womelsdorf, et al. 2006) supports the notion that phase-synchronization reflects information exchange, the role of cross-frequency interactions needs to be explored in greater detail.

Our framework also predicts that the oscillatory dynamics can prevent the transfer of information from region B to C. This is achieved by strong alpha oscillations in B which are in asynchrony or anti-synchrony with oscillations in C. This results in the hypothesis that (i) alpha

power is strong in task-irrelevant areas (i.e. B) and (ii) there is a change in the phase relation between task-irrelevant (B) and downstream regions (C). This might be reflected by anti-synchrony or a decrease in synchrony (possibly due to a change in frequency in one of the pool). The power increase and synchrony decrease will be associated with less inter-areal power-correlation or coherence in the gamma band.

There is strong support for alpha magnitude increasing in task-irrelevant regions during attention and memory tasks (Banerjee, et al. 2011, Bonnefond and Jensen 2012, Foxe, et al. 1998, Payne, et al. 2013, Snyder and Foxe 2010, Thut, et al. 2006, Worden, et al. 2000). For instance, alpha oscillations have been shown to increase in the early visual regions in anticipation of a distractor in working memory tasks (Bonnefond and Jensen 2012, Payne, et al. 2013). With respect to the inter-regional phase relationship, anti-synchrony (~180° phase difference) between parietal and frontal areas during an oculomotor, delayed-match-to-sample task has been reported (Dotson, et al. 2014); however there are also findings demonstrating a decrease in synchronization between visual regions when spatial attention is directed away (e.g. Bastos, et al. 2015, Saalmann, et al. 2012) .

Future investigations are required to identify when and where the mechanisms for preventing information transfer are at play.

Prediction 3: To allow communication between two specific pools of neurons, alpha oscillations must be modulated locally on a fine spatial scale.

The framework proposes that alpha oscillations are differently modulated in neuronal pools A and B (see figure 1c). This should be the case even if the stimuli processed by A and B are close to each other in retinotopic space. This results in the hypothesis that alpha oscillations must be modulated locally.

However, while it is often assumed that alpha oscillations in the visual system are modulated more globally (Thut, et al. 2006), recent monkey and human ECoG data provide promising evidence that alpha oscillations can be modulated locally even at the receptive field level. More precisely, these studies have shown that alpha oscillations increased (compared to baseline) in the surround area of the stimulated receptive field in V1 (Harvey, et al. 2013, van Kerkoerle, et al. 2014). This does not preclude the need for alpha oscillations to be modulated

more globally in the visual system in some situations such as during working memory maintenance to protect against distractors (Bonnefond and Jensen 2012) or during alertness (Sadaghiani and Kleinschmidt 2016).

Communication based on nested oscillations could be a general mechanism throughout the brain

Thus far, we have focused on the coordinating role of alpha oscillations in the visual network. Further modulation of the alpha activity related to functional inhibition has been reported in the language network in humans (Wang, et al. 2012), in pre-frontal regions in the monkey (Buschman, et al. 2012, Engel 2012, Jensen and Bonnefond 2013, Welberg 2013) and even the hippocampus (Staresina, et al. 2016; but see below for a discussion regarding the hippocampus). However, similar functional roles may be played by oscillations at other frequencies, which have been shown to be prominent in other brain regions. For instance, there is strong evidence for the coupling in the theta band between the hippocampus and other regions such as prefrontal cortex, amydala and the striatum (e.g. Backus, et al. 2016, Benchenane, et al. 2010, Kaplan, et al. 2014, Seidenbecher, et al. 2003, Staudigl and Hanslmayr 2013). Importantly when theta and alpha activity are observed in intracranial recordings across species, gamma power is typically found to be coupled to the phase of these oscillations (Belluscio, et al. 2012, Canolty, et al. 2006, Canolty and Knight 2010, Colgin, et al. 2009, Hermes, et al. 2014, Jensen and Colgin 2007, Spaak, et al. 2012, Voytek, et al. 2010). Thus, theta oscillations may play the same functional role as the alpha oscillations in coordinating neuronal processing. Several studies also points to theta being inhibitory (Mehta, et al. 2002). Given that theta oscillations in the monkey hippocampus have been found to overlap in frequency with alpha oscillations (Jutras, et al. 2013), it remains an exciting possibility that the visual cortex and the hippocampus communicate via synchronization by means of these oscillation (Fell, et al. 2011). However, it is debated whether the human theta rhythm is at ~3 Hz or in a higher band (Watrous, et al. 2013). In case it would be at 3Hz, the interactions between the visual cortex and hippocampus could then occur via cross-frequency coupling (Gu, et al. 2015). The involvement of theta oscillations for coordinating the interactions between the striatum and the cortex during motor behavior in rats has been revealed by von Nicolai et al. (2014). In line with the current model, they further

showed that the coordination of fast oscillations occurred via the coherent coupling of theta-phase and high frequency amplitude.

Beta band oscillations might also play a role for coordinating the information flow by means of cross-frequency coupling in e.g. the motor network (van Wijk, et al. 2016). Moreover, some studies have reported attentional modulation of feedback-related beta oscillations in the visual system (e.g. Bastos, et al. 2015, Kornblith, et al. 2016). It remains to be explored what the functional differences between alpha and beta oscillations are. In particular, it will be important to determine whether the beta activity in some cases result from non-linear addition of different alpha generators in different cortical layers (Jones, et al. 2009). In line with this idea, laminar recordings have only revealed modulation of alpha oscillations in the visual system during attentional tasks (e.g. Bollimunta, et al. 2011, van Kerkoerle, et al. 2014) while EcoG recordings have revealed modulation of beta oscillations (Bastos, et al. 2015).

Exchange of phase encoded information

Extensive work in the rat hippocampus has demonstrated that different information is encoded at different phases of the theta cycle. In particular when a rat traverses a place field, the phase of firing of the respective place cell advances with respect to theta-phase (O'Keefe and Recce 1993). Several mechanisms have been proposed for how such a phase-organized code might emerge (Burgess and O'Keefe 2011, Jensen and Lisman 1996, Lisman and Jensen 2013) . In analogy, Jensen et al. (2014) recently proposed a model for how visual information might be encoded along the phase of the alpha cycle. In the model, competing visual representations are represented at different phase of the alpha cycle in order to resolve the bottleneck problem in the visual system. Due to the convergence in the hierarchy of the visual ventral stream, two stimuli (e.g. faces) might partly share the same neuronal representation in higher-order visual areas. Jensen et al. proposed that the processing of these two stimuli is segmented in time by being represented at different phases of the alpha cycle. The stronger the excitability of a given representation the earlier it overcomes the inhibition as it ramps down within an alpha cycle. This creates a temporal code organized according to excitability (Jensen, et al. 2014). As proposed for the hippocampus (Colgin 2011, Jensen 2001), the exchange of phase-encoded information can be achieved by phase-synchronizing the communicating networks (see figure 3).
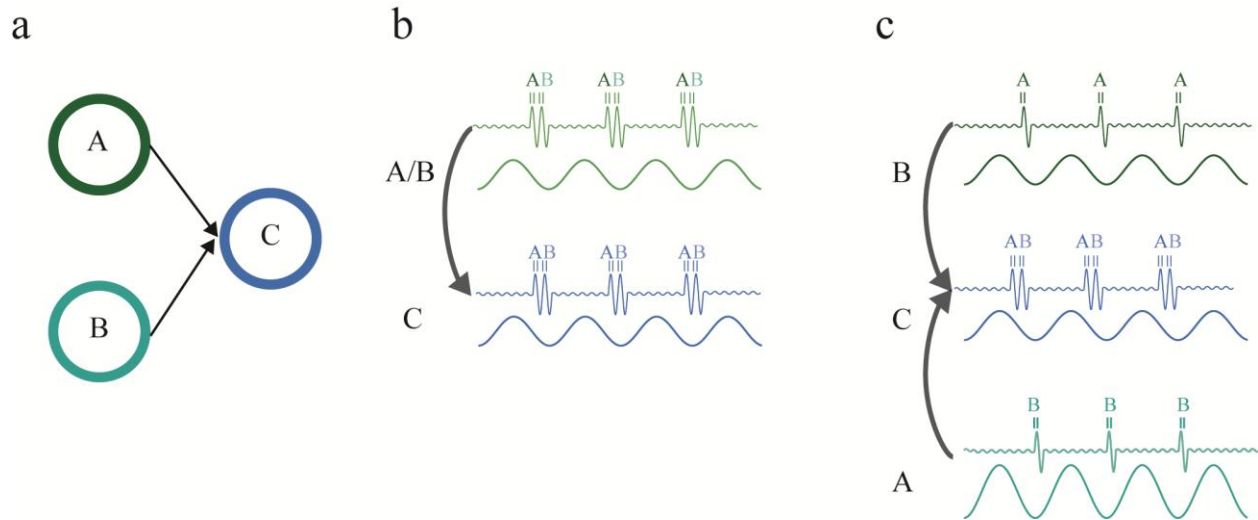
Figure 3: Exchange of phase coded information. **a.** Two stimuli processed by two pools of neurons A and B, e.g. in V1. The pools both project to a pool of neurons C downdstream in the hierarchy, e.g. in V4. Because of this bottleneck in the visual system, it is important that neurons coding for A and B in V1 are not activated simultaenously. For the information related to the two stimuli to be transferred from V1 to V4, we propose two mechanisms **b**. A single alpha generator in V1 controls for the timing of activation of neurons in pool A and B as reflected in the gamma band. The activation of the most excitable neurons, i.e. cells in pool A, overcomes the pulse of inhibition early in the alpha cycle followed by neurons in pool B (see Jensen et al. 2014 for details). The temporal organisation is then transmitted to the pool of neurons in C. **c**. Another possibility is that the magnitude of the alpha oscillations is modulated locally and is lower for one of the representations compared to the other. Since the alpha inhibition is lower for A, the respective neurons fire earlier than B. This temporal organization is then transmitted to C.

Consider two representations associated with neurons in pool A and B. The excitability is stronger for A than for B (figure 3a). Jensen et al. (2014) proposed that the neuronal firing associated with each stimulus occurs at different phases of the alpha cycle. Moreover, A, B and C would be synchronized in the alpha band and, as a consequence, this temporal organization would then be transmitted to C (figure 3b). A possibility Jensen et al. (2014) did not discuss is that the magnitude of the alpha oscillations in the two pools determines which stimulus is processed first (figure 3c). In particular alpha power will be lower in pool A than in pool B, if the stimulus processed by the former is more relevant/salient. As a consequence, the gamma burst will occur earlier in A than in B due to the stronger alpha inhibition in the latter. Importantly, alpha oscillations are still expected to be synchronous between the three pools. To date there is little empirical evidence demonstrating that alpha phase organizes neuronal coding. There is work in the delta, theta and beta band demonstrating phase-coding (Kayser, et al. 2009, Voytek, et al. 2015, Watrous, et al. 2015). We call for future studies in which a phase-specific code is investigated in the visual system in the alpha band.

Control of alpha oscillations in relation to cortical layers

The framework we propose assumes that alpha oscillations are internally controlled in terms of phase and magnitude. We here discuss the mechanisms involved in the control. The control serves to phase-synchronize the oscillations between different regions and to modulate the degree of pulsed inhibition in order to allocate computational resources. A number of studies have shown that alpha magnitude and phase can be modulated in anticipation of relevant or irrelevant stimuli (Bonnefond and Jensen 2012, Foxe, et al. 1998, Foxe and Snyder 2011, Samaha, et al. 2015, Thut, et al. 2006, but see van Diepen, et al. 2015) indicating that alpha oscillatory activity is indeed under internal control. In this section, we discuss two complementary mechanisms for this control, namely that alpha oscillations are controlled by neocortical feedback connections or by the thalamus. We will discuss this in the context of layer-specific computations.

*Feedback in relation to cortical layers and canonical microcircuits*

Interestingly, the pools of neurons involved in the feedforward and feedback pathways are segregated in different cortical layers in the visual system (Markov, et al. 2014). The cortical layers involved in the feedforward and feedback differ according to the hierarchical distance between the connected brain regions (Barone, et al. 2000, Markov, et al. 2011, Markov, et al. 2014). In the case of the connections between V1 and V4, the feedforward pathway originates in supragranular layers (L3B) in V1 and target granular layers (L4) and L3B in V4. The feedback pathway from V4 originates in the supragranular layers L3A and infragranular layers L6 and target supragranular layers L1-2/3A and infragranular layer L6 respectively in V1 (figure 4). Interestingly, alpha activity has been observed mainly in both the supragranular and infragranular layers of a given area, with a stronger power in the later (but see Haegens, et al. 2015) while gamma activity has been shown to be prominent in the granular and supragranular layers (Bollimunta, et al. 2008, Bollimunta, et al. 2011, Buffalo, et al. 2011, Dougherty, et al. 2015, Maier, et al. 2011, Spaak, et al. 2012, van Kerkoerle, et al. 2014).

According to our model, supragranular and/or infragranular alpha oscillations should exercise an inhibitory phasic influence on the granular and/or the supragranular gamma magnitude (see Spaak, et al. 2012) (figure 4b).

As shown in figure 4, the feedback is diverging when originating in V4 and project back to several V1 regions. This feedback needs to be selective, e.g. determining the alpha phase synchronization from C to A, but not C to B. Moreover, local alpha magnitude in A and B should be distinct with a higher alpha magnitude in B. We discuss below the putative role of different neocortical and subcortical regions in modulating the local change in alpha magnitude and the alpha synchronization between communicating areas.

It remains to be better understood how alpha and gamma oscillations are generated from a physiological perspective and how their interaction is implemented at the level of the microcircuit. The mechanisms generating gamma oscillations have been extensively reviewed in Buzsáki and Wang (2012) but less is known about alpha oscillations. Alpha oscillations are thought to involve inhibitory neurons to set-up pulses of inhibition every ~100ms. Somatostatin cells engaged via lateral connections (Zhang, et al. 2014) or trans-laminar fast-spiking neurons engaged by layer 6 neurons (Bortone, et al. 2014, Olsen, et al. 2012) or even layer 5 pyramidal cells (Buchanan, et al. 2012) are strong candidates but further research is needed to evaluate their behavior during alpha oscillations. Layer 1 interneurons might also be involved as dendrites from layers 2/3A, 3B and 5 reach this layer (Markov, et al. 2014). Also, the role of lateral connections (Angelucci and Bullier 2003, Tamura, et al. 2004, Wang, et al. 2000) as well as the role of the thalamus (da Silva, et al. 1973, Lorincz, et al. 2009, Vijayan and Kopell 2012) needs to be investigated.

The examples considered here concern the visual system. It has, however, been shown that the laminar organization (e.g. cortical types can be granular, agranular or dysgranular) and the connectivity between areas varies across networks (see e.g. Rempel-Clower and Barbas 2000). It will be important to consider these anatomical, but also functional, heterogeneities to further determine whether the information is communicated by similar principles in these different networks.
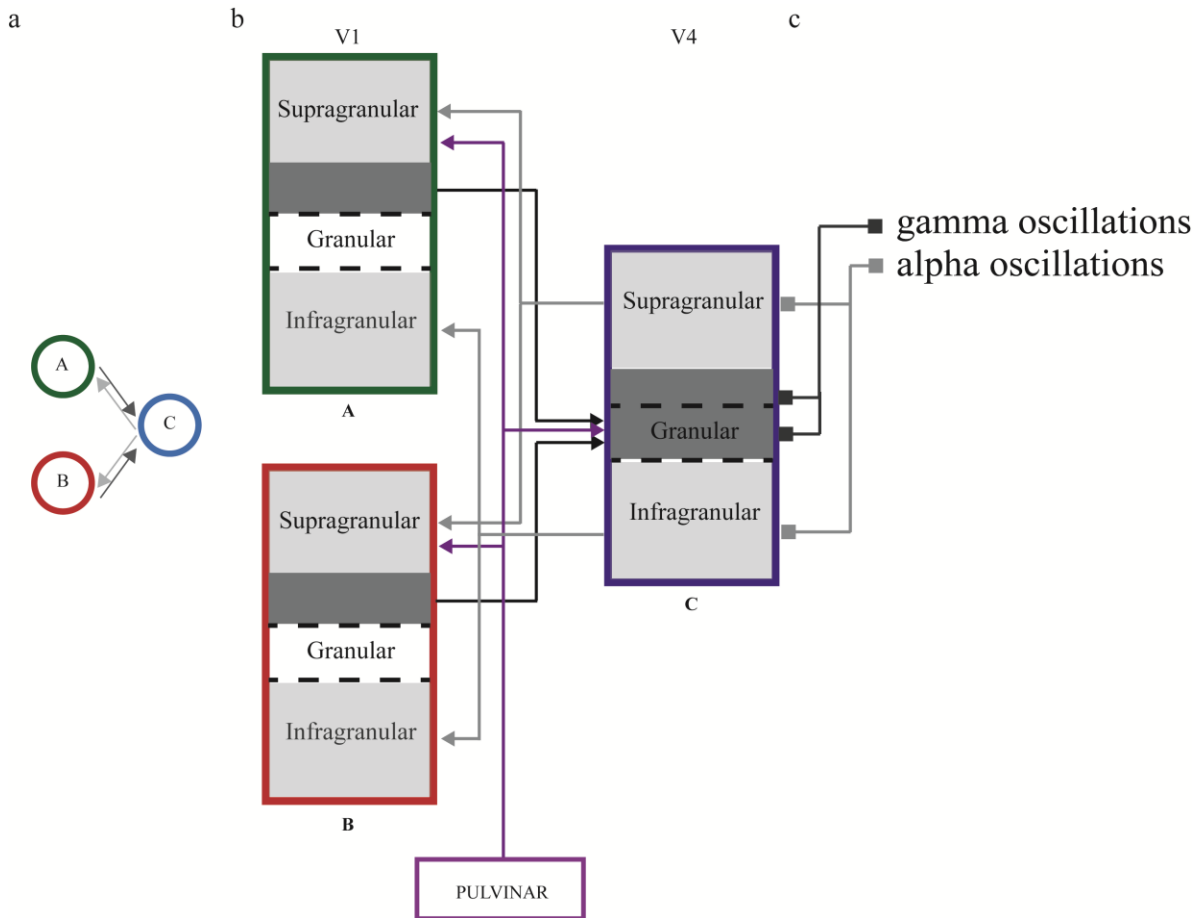
Figure 4: Converging feed-forward and diverging feedback pathways. **a.** Pools of neurons A and B converge on a pool of neurons in C. Black arrows represent the converging feedforward pathway while the grey arrows represent the diverging feedback pathway **b.** Example in which two cortical columns in V1 (A,B) are connected to a column in V4 (C). Three layers are represented, the supragranular, the granular and the infragranular layers. In dark and light grays are represented in the layers involved in the feedforward and feedback pathways respectively. The layers associated with each pathway are inspired by Markov et al. (2014). The feedforward connections from the pulvinar are also indicated (purple arrows) **c**. Gamma and alpha oscillations have been shown to be prominent in the granular/supragranular and infragranular/supragranular layers respectively.

Regions involved in the control of alpha

Several studies have investigated the influences of the fronto-parietal network, i.e. the frontal eye field (FEF) and the posterior parietal cortex, on activity of posterior regions (Noudoost and Moore 2011, Squire, et al. 2013, Szczepanski, et al. 2010). The fronto-parietal network includes a number of areas that are retinotopically organized, and it is engaged during spatial attention, saccade planning and other cognitive and perceptual operations (Saygin and Sereno 2008, Silver and Kastner 2009). The fronto-parietal network is directly and indirectly (through the pulvinar) connected to visual regions. The FEF and parietal cortex have both been shown to be associated with the control of alpha activity in posterior regions in humans

(Capotosto, et al. 2009, Marshall, et al. 2015, Sauseng, et al. 2011) potentially via the superior longitudinal fasciculus (Marshall, et al. 2015). However, the role of the fronto-parietal network for controlling alpha phase remains to be elucidated (but see Sauseng, et al. 2005).

Recently, Sadaghiani et al. (2016) further proposed that different cortical networks were involved in controlling alpha oscillations. More specifically, they proposed that a network including the dorsolateral prefrontal cortex, the rostrolateral prefrontal cortex, the posterior inferior parietal lobe, the paracingulate gyrus, and there mid-cingulate gyrus was involved in controlling long-range alpha phase-locking associated with adaptative control while the dorsal attention network (including intraparietal sulci, frontal eye fields, and middle temporal complex) was associated with controlling the (dis-) engagement of regions via the control of local alpha amplitude and as such with implementing selective attention.

Subcortical regions might also play a key role in modulating alpha activity. For instance, the pulvinar is in a particularly well-suited anatomical position for controlling the communication between posterior neocortical areas, since it is connected to a wide range of areas in the visual hierarchy. More specifically, it is connected to neighboring cortical regions that are themselves directly connected to each other (Saalmann and Kastner 2011, Saalmann, et al. 2012). Here, we consider two ways in which the pulvinar might influence the synchronization in the alpha band between brain regions:

(**1**) The pulvinar might modulate the feedback originating from higher-order regions as it targets layers 1 to 3 (L 1-3) of the lower-order area. In line with this idea, Purushothaman, et al. (2012) showed that electrical stimulation of pulvinar neurons in anesthetized prosimian primates resulted in boosting the firing of V1 neurons when stimuli were presented in the V1 neurons' receptive fields, while it suppressed the neuronal activity when the stimuli were presented outside the receptive field. As such, the stimulation mimicked the effects of attention. Following the schema shown in Figure 4, we suggest that the pulvinar serves to synchronize C and A by increasing the impact of the feedback connections arriving in L1-3. Likewise, the pulvinar might decrease the activity in B reducing the synchrony between C and B. It is further possible that the pulvinar increases the magnitude of alpha oscillations in B.

(**2**) The pulvinar might directly control the synchronization of alpha activity between two areas, as it is connected to supragranular layers (L1-3) of the lower-order area (e.g. V1) and granular layer (L4) of the higher-order area (e.g. V4) (Saalmann and Kastner 2011). Although

alpha activity is thought to be particularly high in supragranular and infragranular layers, several papers have also revealed the presence of an alpha generator in L4 (Bollimunta, et al. 2008, Bollimunta, et al. 2011, Haegens, et al. 2015). It is thus possible that the pulvinar allows the synchronization between L1-3 in a lower-order region and L4, which receives the feedforward activity, in a higher-order region. In line with this idea, Saalmann et al. (2012) demonstrated, using a measure of Granger causality, that the pulvinar was driving the alpha-band synchronization between V4 and TEO when attention was allocated at the receptive field of the regions recorded. However, they did not observe an increase of the amplitude of alpha oscillations in these cortical areas when attention was directed away from it (Kastner, unpublished observations). Such amplitude change might occur only in V1. Therefore, they could not investigate the influence of the pulvinar on a change in alpha amplitude as suggested in the paragraph above. Interestingly, the pulvinar is also known to be connected to frontal areas (Saalmann and Kastner 2011). It is therefore possible that part of the influence of frontal areas on the sensory cortex are mediated by the pulvinar. In summary, the mechanisms underlying the influences of the pulvinar on alpha oscillations in the different cortical areas remain to be understood. In addition to the pulvinar, interactions between the prefrontal cortex, the thalamic reticular nucleus (TRN) and the lateral geniculate nucleus might also be involved in setting-up alpha power increases in early visual regions. Recent papers have shown that the prefrontal cortex directly influences TRN activity, thereby controlling thalamic sensory gain during attention (Halassa, et al. 2011, Wimmer, et al. 2015).

Further investigations, such as exploring the task-specific laminar profiles of alpha oscillations will be necessary to determine how the feedback activity from higher visual regions and the different cortical and subcortical regions influence the power and the phase of alpha activity across the visual network. In particular, it will be useful to determine how the phase synchrony (both synchrony and anti-synchrony) is implemented. It is possible that the alpha oscillations observed in different layers have distinct roles for coordinating communication. For instance, alpha in supragranular layers might be involved in coordinating inter-areal communication over long distances, while alpha in infragranular layers might be involved in more local control of granular and supragranular gamma power. Indeed, it has been shown that the supragranular layers exhibit a spatially-specific connectivity in both the feedforward and feedback pathways, while the infragranular layers exhibit a more diffuse connectivity (Markov,

et al. 2014). The more diffuse connectivity might be related to the role of alpha oscillations in the inhibition of all non-relevant cortical columns in a rather unspecific way while the spatially-specific connectivity could be related to the communication of alpha activity within the relevant pools of neurons.

The role of saccades and slower rhythms

In most electrophysiological studies in human and animals on attention and visual perception, fixation is kept constant. However in daily life we make saccades several times per second. Furthermore, even when fixating micro-saccades at 3 – 4Hz are apparent (Bosman, et al. 2009, Lowet, et al. 2016). In future work, it will be of great interest to investigate how saccade relates to coupled alpha and gamma oscillations. One intriguing possibility is that the (micro-) saccades are coordinated with alpha oscillations (Drewes and VanRullen 2011, Gaarder, et al. 1966). While spatial sampling could involve saccades, it could as well be implemented by rhythmic shifts of spatial attention at slow frequency (Fiebelkorn, et al. 2013, Landau and Fries 2012, Landau, et al. 2015, Song, et al. 2014, see VanRullen 2016 for a review).

In the latest version of the CTC, Fries (2015) further develops the idea that the cross-frequency coupling between theta and gamma oscillations implements visual attentional sampling (Bosman, et al. 2009, Bosman, et al. 2012). The sampling role of theta oscillations in the visual system proposed by Fries (2015), which seems to be transmitted in the feedforward direction (Bastos et al. 2015, van Kerkoerle et al. 2014), is different from the role of alpha oscillations we propose. Specifically we suggest that the role of alpha oscillations is to implement inter-areal communication by modulating inter-areal phase synchronization and the local magnitude. However, recent results suggest that the theta and alpha rhythms could interact. Song et al. (2014) presented interesting results showing that the behavioral performances (in terms of reaction time) in an attention task (discrimination of a square or a circle) was modulated in the alpha-range, but alternated between the cued and uncued side at a theta rhythm (3-4Hz), i.e. the behavior exhibited a theta-alpha coupling.

Further work is needed to understand in which situations such slower rhythms are required and how they interact with the alpha and gamma oscillations in relation to (micro-) saccades. Finally, it is important to develop a model integrating the feedforward sweep that is evoked by saccades and microsaccades (Gaarder, et al. 1966, Ito, et al. 2013).

Conclusion

In this paper, we have proposed a framework for flexible communication between interconnected nodes in the brain based on the coupling between slow oscillations in the theta/alpha band and activity in the gamma band. Testing the framework will require integrating animal and human research in order to relate spiking to behavior from a mechanistic perspective. This will allow for elucidating how representational specific information is exchanged between brain regions. Finally, it needs to be understood how these cross-frequency interactions are internally controlled. Of particular interest is the involvement of the thalamus in coordinating oscillatory activity between regions.

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