On the operation of visual cortical gamma in the light of frequency variation

Chapter 8: Summary and Conclusions

The primary aim of this thesis is to understand the mechanisms and the significance of the frequency variations of gamma oscillation for its synchronization behavior and for information processing, using theoretical as well as experimental techniques. We had to integrate our theoretical approaches with empirical targeted neurophysiological experiments in monkeys, to test model predictions in empirical data. Contrary to currently emerging views that seemingly random variations in frequency render gamma useless for encoding and neuronal communication (Burns et al., 2011; Ray and Maunsell, 2010), our work indicates that frequency variation in the visual cortical gamma rhythm is essential for understanding how synchronization may contribute to the encoding of input (as well as to neural communication within and between cortical areas).

In the experimental work using LFP/CSD simultaneous recording in macaque visual areas V1 and V2 (Chapter 2), we show that the frequency of gamma oscillations in V1 and V2 shifts in a similar manner with stimulus grating contrast. Moreover, the frequency of V1 and V2 gamma oscillations always matched over the different conditions and on a moment-by-moment basis (single trial dynamics). Importantly, despite stimulus-driven changes in gamma frequency and despite momentary frequency variations at a fixed contrast, V1 and V2 gamma showed substantial coherence. The manner in which coherence emerged was in line with anatomical expectations. In particular, V1 gamma oscillations influenced V2 gamma in a feed-forward manner and exhibited a laminar-specific coherence pattern across the cortical areas in line with anatomically described feedforward connectivity. This work showed that despite of the important variation of gamma frequency, spatially separated cortical network can maintain coherence. This contradicts previous suggestions and views that this variation would prevent meaningful inter-areal communication (Burns et al., 2011; Ray and Maunsell, 2010). Instead, our data suggested an active mechanism by which gamma frequency was matched in order to permit synchronization and neural communication.

The gamma frequency dependency on visual contrast, demonstrated in monkey microelectrode recording, could be confirmed in the human primary visual cortex using magneto-encephalography (MEG) as well (Chapter 3). Similar to the monkey early visual cortex, the frequency increased with visual contrast in human visual cortex. In addition, we showed that gamma power increased with contrast, yet in contrast to macaque cortex, without a saturation component. Furthermore, we described for the first time systematic asymmetries in the power spectral profile of gamma oscillations. This work extends the work done on monkey visual cortex to human visual cortex, and is important as theoretical models on gamma synchronization described in monkeys (see chapters 5 and 7) are likely to also apply to humans.

One of the features of gamma brought to the foreground in the empirical work in the first two chapters, pointed towards the presence of strong V1/V2 gamma frequency variation over time within a particular condition. To improve understanding of these fast time-scale variation, we analyzed the V1-V2 neural data from Chapter2 with the aim of understanding whether the seemingly random frequency fluctuations (as described by (Burns et al., 2011) is instead structured by other brain processes (Chapter

4). We found that gamma frequency fluctuations are temporally structured with a rhythmic component showing peak power in the 3-4Hz range (low theta band). By theta-windowing analysis, we showed that the frequency, the power as well as the coherence between V1 and V2 gamma is modulated by a low theta rhythm. In addition we showed that this low theta rhythm is closely related to fixational eye movements (micro-saccades) that occur 3-4 times per second. This work showed that rapid fluctuations of gamma frequency are not random, but instead are complex and systematically depending on slower time-scale rhythmic fluctuations.

In Chapter 5 numerical simulation techniques were used to study the role and implication of systematically changing oscillation frequency. We used conductance-based neuronal models (Hodgkin-Huxley equations) to simulate excitatory-inhibitory networks. In addition, we used an abstract phase-oscillator model (that can be used for analytical analysis) to represent the essential dynamics occurring in the complex excitatory-inhibitory networks. We found that oscillation frequency, modulated by input variations among neighboring neuronal pools, is a critical variable to determine phase-locking as well as phase-relation among those locally connected neurons. We systematically described the relation of phase-locking, frequency and phase-relation and found that the weakly coupled oscillatory theory (TWCO) could well explain the synchronization patterns emerging in response to distributed patterns of input to the network. Our simulations showed that the specific synchronization response to distributed input to a neural network, which consisted of predictable frequency and phase relations among local units in the network, effectively captured the properties of the input. Hence, the performed simulations show that frequency variations, rather than being detrimental, are useful for information processing. Moreover, a subset of the simulations also directly demonstrated how the TWCO based networks showed self-organization into synchronization fields that could be useful feature integrations in natural visual scenes. This simulation hence supports the idea of a 'local' version of binding theory (see Introduction).

The TWCO based simulations, the assumption is made that weak coupling can be compared to horizontal connectivity among columns, and that input sets intrinsic frequency. While the performance I these networks in encoding input seemed promising in simulations, we aimed to test the clear predictions on the properties of synchronization in experimental data. As our recordings and simulations revealed the non-stationary nature of gamma, we anticipated that we would need a new method for analyzing phase relations in empirical recording data. To that aim, we first tested whether standard oscillatory synchronization detection methods are trustable for fast-varying oscillations. Hence, in Chapter 6 we studied the implication of fast-varying frequency and power fluctuation of gamma oscillations for commonly used phase-locking measures (coherence) that are based on the Fourier Transform. Commonly used Fourier-based phase-locking methods assume stationarity which is violated by these rapid fluctuations. We show how badly Fourier-based phase-locking methods fail when applied to non-stationary data, and document the underlying reasons why under these circumstances these commonly used methods fail. In this work, the concept of non-stationarity is developed, and demonstrated in the form of the partially synchronized state, which is characterized by the occurrence of phase-relation dependent frequency fluctuations (PrFM). Although in general it may be considered a given that Fourier based phase locking methods should not be applied to non-stationary data, these methods are commonly used without verification of non-stationarity, and in the face of the large probability that in fact the data will be non-stationary. As an alternative approach, we suggest to use non-stationary methods based on the Hilbert Transform or Wavelet Transform. We show as a concrete alternative the results from a combined application of singular-spectrum decomposition (SSD) and Hilbert Transform. This approach clearly yielded superior results compared to common stationary methods in determining the correct phase-locking value.

In Chapter 7, we used experimentally controlled spatial contrast variations to manipulate intrinsic frequency variations across the retinotopic map of macaque V1, and measured the effects of these frequency variations on synchronization behavior for varying distances among local pools of neurons exposed to these different input levels. This was achieved by simultaneously recording with three laminar probes in macaque visual cortex V1 for various variations in local stimulus contrast. In this experimental setup, we aimed to test the precise predictions from TWCO regarding the emergence of specific frequencies as well as modulations of phase-locking and phase-relations of gamma oscillations as a function of intrinsic frequency differences (i.e. set by stimulus input). The results show for the first time that cortical gamma oscillations behave in accordance to the predictions of the weakly coupled oscillator theory (by reconstructing the Arnold tongue). In addition, we show for the first time the existence of partially synchronized state in gamma oscillations and the presence of phase-relation dependent frequency fluctuations (PrFM), necessitating the use of non-linear approaches for the estimation of phase locking.

The most important contributions of the thesis to the current literature are the following. First, the work presented in the thesis demonstrates, in accordance with recent reports from other labs (Burns et al., 2011; Jia et al., 2013; Ray and Maunsell, 2010), that oscillation frequency rapidly fluctuates over time and changes systematically with stimulus input and other experimental manipulations (and induced cognitive states). However, we found that the frequency fluctuations are structured, shaped by the oculomotor system, and shared among interacting visual cortical areas. This underlines the importance of distinguishing truly (non-deterministic) random processes from processes which are highly complex, yet deterministic. Second, our work underlines the necessity to use spectral data analysis methods that can capture the fast dynamics and complexity that we have shown to be present in what can be considered typical LFP data. These methods, such as the SSD/Hilbert-based methods we contributed, should not assume stationarity and preferably should capture linear as well as non-linear components. Third, starting from our own observations and that of other labs showing that neural gamma oscillations adapt their frequency in an input-specific manner, we investigated according to which theoretical models this input dependency of gamma could be exploited by the brain for computation. We showed theoretically as well as experimentally that frequency variations are critical for determining the phase-locking and phase-relation among synchronizing neurons. The combined theoretical and experimental analysis performed, identified the mathematical principles of TWCO as determining synchronization behavior. This represents an important step forward in moving from a descriptive analysis of synchronization towards an analysis of mathematical principles with predictive power. Fourth, as a direct result of identifying a mathematical model that provides principles of synchronization, the presented work also puts a more realistic scope on the contribution of gamma in encoding, limiting it to (local) interactions among neurons that are closely connected to each other. Fifth, with respect to the discussion in the literature whether synchronization of spikes or spike time differences are important for neural coding, the present work shows that both parameters, namely phase-locking (spike synchrony) and phase-relation (spike timing), can be seen as important for understanding the mechanism of neural coding (Buehlmann and Deco, 2010; Caporale and Dan, 2008; Hopfield and Brody, 2001; Ritz and Sejnowski, 1997; Stanley, 2013; Tiesinga et al., 2008). Sixth, we directly demonstrated in our empirical data the existence of the partially synchronized state, which is associated with small frequency differences. This has not only implications for data analysis (see point two), but also invites a rethinking of the concept of synchronization and how it contributes to neural processing and coding. In the partially synchronized synchronization regime, which is predicted by TWCO, oscillators are neither completely synchronized nor asynchronous, but exhibit periods of 'phase-locking' intermixed with periods of fast phase precession. This type of synchronization induces rapid phase-relation dependent frequency and amplitude fluctuations. This synchronization regime, in line with the concept of criticality (Beggs, 2008; Daido, 1990; Yang et al., 2012), is not an undesirable or imperfect state of synchronization, but rather a regime (between complete order and disorder) that permits fast and flexible changes in synchronization patterns when input of brain state is changing. The system is neither in complete synchrony (as occurring during epilepsy) where differences are minimized and the information capacity is small, nor in complete asynchrony (random phase-relations) where information cannot be encoded. This in-between regime, which on the surface appears complex and random-like, is instead inherently systematic and structured, and might be considered 'meaningful', as suggested in various other systems (Bak et al., 1988). The flexibility of the partially synchronized state can also be understood in the context of attractor states in neural network functioning. In a partially synchronized state, the activity pattern in the system is influenced by an 'attractor state' but not completely captured by it, so that it can more easily switch from one attractor state to another (Eliasmith, 2005).

Taking all of these points together, our work demonstrates, seemingly counter-intuitively, that small frequency differences among interacting oscillations, is not detrimental but instead critical for establishing meaningful synchronization patterns that are flexible enough to represent fluctuating inputs and brain states, and hence that are useful for neural computation. We suggest that the conceptual advances made by the work included in this thesis will provide a basis to better understand the role of oscillatory synchronization for information processing, transmission and learning in visual and other systems.

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