

# 1 **Neuronal gamma-band synchronization regulated by instantaneous** 2 **modulations of the oscillation frequency**

3

4 **Authors:** E. Lowet<sup>1\*</sup>, M.J. Roberts<sup>1</sup>, A. Peter<sup>2</sup>, B. Gips<sup>3</sup>, P. De Weerd<sup>1</sup>

## 5 **Affiliations:**

6 <sup>1</sup> Psychology and Neuroscience, Maastricht University, Maastricht, The Netherlands

7 <sup>2</sup> Ernst Strüngmann Institute (ESI) for Neuroscience in Cooperation with Max Planck Society,  
8 Frankfurt, Germany

9 <sup>3</sup> Donders Institute for Brain, Cognition and Behaviour, Radboud University Nijmegen,  
10 Nijmegen, The Netherlands

11 \*Correspondence to: [elowet@mailfence.com](mailto:elowet@mailfence.com)

12

13 **Neuronal gamma-band synchronization shapes information flow during sensory and**  
14 **cognitive processing. A common view is that a stable and shared frequency over time is**  
15 **required for robust and functional synchronization. To the contrary, we found that non-**  
16 **stationary instantaneous frequency modulations were essential for synchronization. First,**  
17 **we recorded gamma rhythms in monkey visual area V1, and found that they synchronized**  
18 **by continuously modulating their frequency difference in a phase-dependent manner. The**  
19 **frequency modulation properties regulated both the phase-locking and the preferred**  
20 **phase-relation between gamma rhythms. Second, our experimental observations were in**  
21 **agreement with a biophysical model of gamma rhythms and were accurately predicted by**  
22 **the theory of weakly coupled oscillators revealing the underlying theoretical principles that**  
23 **govern gamma synchronization. Thus, synchronization through instantaneous frequency**  
24 **modulations represents a fundamental principle of gamma-band neural coordination that**  
25 **is likely generalizable to other brain rhythms.**

26

## 27 **INTRODUCTION**

28 Synchronization, the ability of oscillators to mutually adapt their rhythms (Pikovsky et al., 2002;  
29 Winfree, 1967), is a ubiquitous natural phenomenon. Neural synchronization in the gamma-range  
30 (25-80Hz) has been reported both in subcortical structures (Akam et al., 2012; Steriade et al.,  
31 1993; Zhou et al., 2016) and in cortical areas (Fries, 2015; Gray and Singer, 1989; Gregoriou et  
32 al., 2009). Gamma rhythms emerge in activated neural circuits, in which fast-spiking inhibitory  
33 neurons play a central role (Cardin et al., 2009; Tiesinga and Sejnowski, 2009; Traub et al.,  
34 1996). A prime example is the emergence of gamma rhythms in the early visual cortex during

35 visual stimulus processing (Brunet et al., 2013; Gail et al., 2000; Gray and Singer, 1989; Hermes  
36 et al., 2014; Ray and Maunsell, 2010; Roberts et al., 2013). Gamma synchronization has been  
37 found to relate to the formation of neural assemblies within (Gail et al., 2000; Gray and Singer,  
38 1989; Havenith et al., 2011; Vinck et al., 2010) and across brain areas (Bosman et al., 2012;  
39 Gregoriou et al., 2009; Jia et al., 2013a; Roberts et al., 2013; Sirota et al., 2008; Zhou et al.,  
40 2016). Precise temporal coordination of presynaptic spikes increases their effectiveness on  
41 postsynaptic targets (Fries et al., 2001; Tiesinga et al., 2005) and can thereby modulate the  
42 effectiveness of neural communication (Börgers et al., 2005; Cannon et al., 2014; Womelsdorf et  
43 al., 2007), as shown between V1 and V4 during visual attention (Bosman et al., 2012; Grothe et  
44 al., 2012). Temporal coordination in terms of spike timing (phase code) might be an efficient and  
45 robust mechanism for information coding (Havenith et al., 2011; Jensen et al., 2014; Maris et al.,  
46 2016; Tiesinga et al., 2008; Vinck et al., 2010). Further, gamma rhythmic inhibition might  
47 increase coding efficiency through sparsening (Chalk et al., 2015; Jadi and Sejnowski, 2014;  
48 Vinck and Bosman, 2016) and normalization (Gieselmann and Thiele, 2008; Ray et al., 2013) of  
49 neural activity. These network consequences of gamma have led to influential hypotheses about  
50 the function of gamma for sensation and cognition (Buehlmann and Deco, 2010; Buzsáki and  
51 Wang, 2012; Eckhorn et al., 2001; Fries, 2015; Gray and Singer, 1989; Maris et al., 2016; Miller  
52 and Buschman, 2013), including a role in perceptual grouping (Eckhorn et al., 2001; Engel et al.,  
53 1999; Gray and Singer, 1989) and in visual attention (Bosman et al., 2012; Fries, 2015;  
54 Gregoriou et al., 2009; Miller and Buschman, 2013).

55 Surprisingly, in spite of important scientific advances, it is not well understood how  
56 gamma rhythms synchronize and what the underlying principles of synchronization are. For  
57 example, recent experimental observations of large variability of the precise oscillation  
58 frequency have raised doubts on the robustness and functionality of gamma synchronization in  
59 the brain. It has been observed that the precise frequency fluctuates strongly over time (Atallah  
60 and Scanziani, 2009; Burns et al., 2011, 2010) and that different cortical locations can express  
61 different preferred frequencies (Bosman et al., 2012; Ray and Maunsell, 2010). That these  
62 observations have led to doubts on the functionality of gamma synchronization indicates that  
63 research into gamma synchronization often starts from the premise that continuously matched  
64 frequencies are a requirement for the occurrence of stable phase-relations. The observation of  
65 frequency variations and frequency differences would then suggest that meaningful  
66 synchronization cannot be maintained. These ideas reveal a stationary view of synchronization,  
67 which assumes that the underlying oscillatory dynamics are stable at a fixed phase-relation and  
68 shared frequency. This is also reflected in the widespread use of stationary methods to assess  
69 gamma synchronization, of which spectral coherence is a prime example (Carter et al., 1973).  
70 From a dynamic systems perspective however, synchronization is primarily a non-stationary  
71 process (Izhikevich and Kuramoto, 2006; Izhikevich, 2007; Kopell and Ermentrout, 2002;  
72 Pikovsky et al., 2002; Winfree, 1967), because oscillators adjust their rhythms through phase  
73 shifts (i.e., changes in the instantaneous frequency).

74 Here, by using a combination of theoretical and experimental techniques, we studied the  
75 dynamical principles of gamma synchronization in monkey visual area V1. We simultaneously  
76 recorded gamma-rhythmic neural activity at different V1 cortical locations and studied their  
77 synchronization properties while using local stimulus contrast (Ray and Maunsell, 2010) to  
78 modulate the frequency difference (detuning). Strikingly, we observed that frequency-variable  
79 gamma rhythms still synchronized, even when the mean frequencies did not match. This was  
80 achieved by continuously varying their instantaneous frequency difference in a manner  
81 depending on the phase difference. The function relating phase difference to frequency  
82 difference had a sinusoidal-like shape. The interplay between the detuning, representing a  
83 desynchronization force, and the amount of instantaneous frequency modulations, representing a  
84 synchronization force, regulated the phase-locking strength and the preferred phase-relation  
85 between V1 locations. Further, detuning was dependent on visual grating contrast difference,  
86 whereas frequency modulation strength was dependent on the cortical distance.

87 To assess the biophysical underpinning of our V1 observations, we simulated two  
88 interacting pyramidal-interneuron gamma (PING) networks (Bartos et al., 2007; Börgers et al.,  
89 2005; Tiesinga and Sejnowski, 2009). In line with our observation in V1, we found gamma  
90 synchronization to be associated with rapid frequency modulations. The modulation strength was  
91 modulated by synaptic connectivity, whereas detuning was dependent on the excitatory input  
92 drive. To achieve a principled understanding of our observations, we applied the theoretical  
93 framework of weakly coupled oscillators (Ermentrout and Kleinfeld, 2001; Hoppensteadt and  
94 Izhikevich, 1998; Kopell and Ermentrout, 2002; Kuramoto, 1991; Pikovsky et al., 2002). We  
95 found that a single differential equation accounted well for the non-stationary frequency  
96 modulations and further allowed for precise predictions of how the phase-locking and the phase-  
97 relation between gamma rhythms changed across conditions.

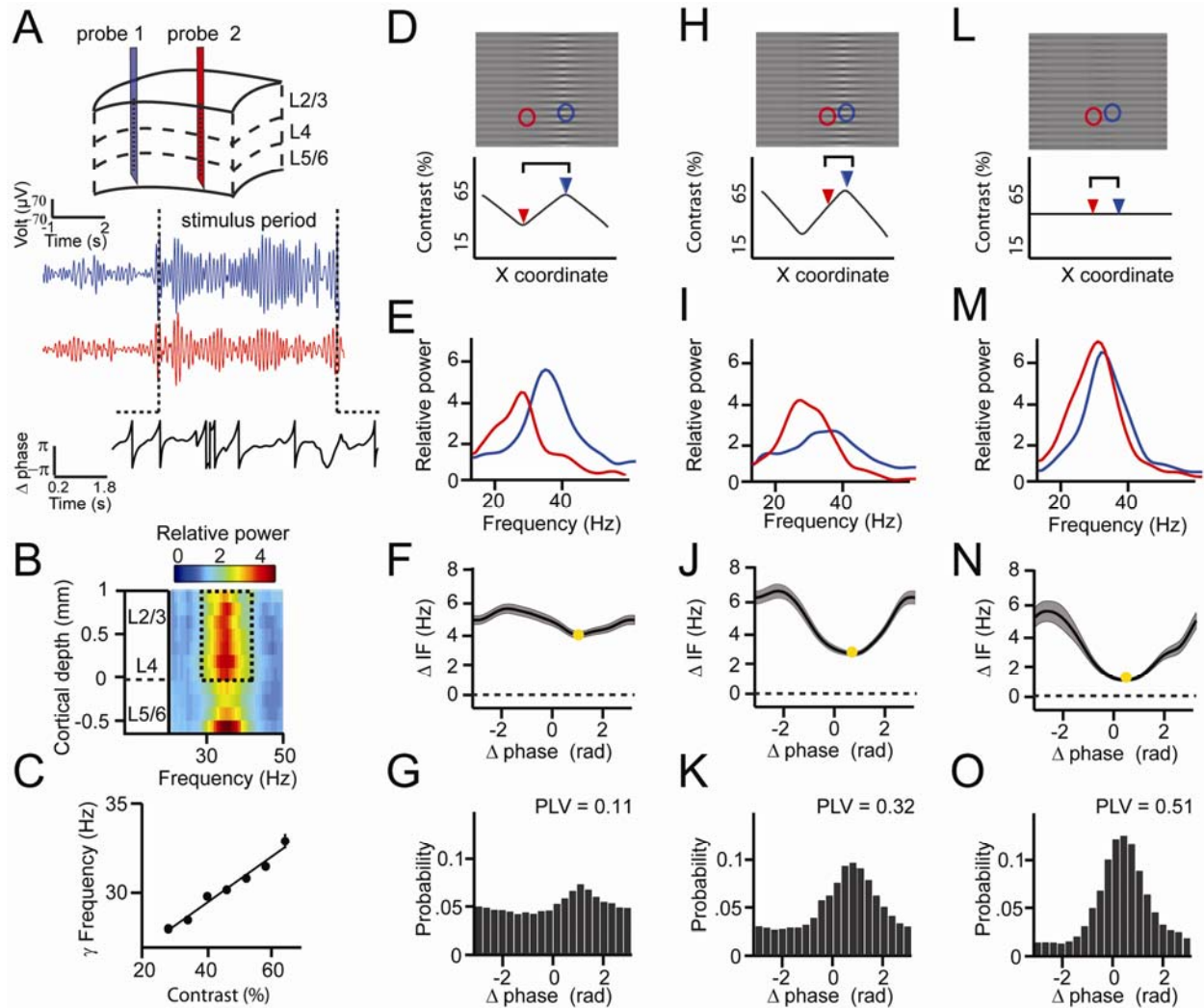
98

## 99 **RESULTS**

### 100 **Local frequency differences regulate the dynamic synchronization process between V1** 101 **gamma rhythms**

102 We first asked how synchronization within V1 was influenced by frequency differences, and by  
103 the distance between recording sites. To this aim, we recorded from 2 to 3 laminar probes  
104 simultaneously in cortical area V1 of two macaques (M1 and M2) (Fig.1A). We used distances in  
105 the order of magnitude of V1 horizontal connectivity (Stettler et al., 2002), hence probes were  
106 separated by 1 to 6mm. Using laminar probes enabled us to reduce the influence of volume  
107 conduction by calculating current-source density (CSD) as a network signal. Using CSD, we  
108 estimated the instantaneous frequency, phase and phase difference of gamma signals. The  
109 monkeys fixated centrally while a whole-field static grating with spatially variable contrast was  
110 shown. Gamma power was induced in layers 2-4 and in the deepest layer (Fig.1B, Fig.S1). V1  
111 locations showed increased gamma frequency with increased local contrast (linear regression,  
112 single contact level, M1:  $R^2=0.38$ , M2:  $R^2=0.27$ , both  $p<10^{-10}$ , Fig.1C, Fig.S2) allowing us to

113 parametrically vary the frequency difference between probes by varying the contrast difference.  
114 We will first show the key results through three illustrative examples. In the first example, we  
115 chose two cortical locations separated by a relatively large distance of ~5mm, presented with a  
116 visual contrast difference of 17% (Fig.1D). Their frequency difference was 5Hz as shown by  
117 their non-overlapping power spectra (Fig.1E). This would imply that the phase difference would  
118 not be constant, but would advance at a phase precession rate of  $2\pi$  every 200ms, which could be  
119 expected to preclude synchronization. However, the frequency difference was not constant.  
120 Instead, the instantaneous frequency difference was modulated as a function of phase difference  
121 (Fig.1F, Fig.S3) with a modulation amplitude of 1Hz. At the smallest frequency difference (4Hz,  
122 yellow point) the phase precession was slowest, at  $2\pi$  every 250ms, meaning that the oscillators  
123 stayed relatively longer around that phase difference. As a result, the probability distribution of  
124 phase differences over time (Fig.1G) was non-uniform giving a phase-locking value (Lachaux et  
125 al., 1999) (PLV) of 0.11. The peak of the distribution, the ‘preferred phase’, was at 1.3rad, in line  
126 with the minimum of the instantaneous frequency modulation function. In the second example,  
127 we chose a pair with a similar frequency difference of 4.8Hz but a closer distance (~2.5mm,  
128 Fig.1H). The instantaneous frequency modulation amplitude was larger with a modulation  
129 amplitude of 1.8Hz (Fig.1J) and a modulation minimum around 3Hz at the preferred phase.  
130 Because phase precession at the preferred phase was slower, the phase difference distribution  
131 was narrower than in the previous example, indicating higher synchrony (PLV=0.32, Fig.1K)  
132 with a peak centered at a different phase (0.78rad). In the third example the cortical distance  
133 remained the same but the frequency difference was reduced (2.8Hz) by eliminating the contrast  
134 difference (Fig.1M, the remaining frequency difference might be due to eccentricity, see Fig.S2).  
135 The frequency modulation amplitude did not change however, with a lower mean difference, the  
136 modulation minimum was close to zero (1Hz, Fig.1N), thus the associated phase difference  
137 (0.48rad) could be maintained for even longer periods and the phase difference probability  
138 distribution was even narrower (PLV=0.51, Fig.1O). The three examples were representative for  
139 the 805 recorded contact pairs in monkey M1 and 882 contact pairs in monkey M2 where each  
140 pair was recorded at 9 levels of contrast difference.

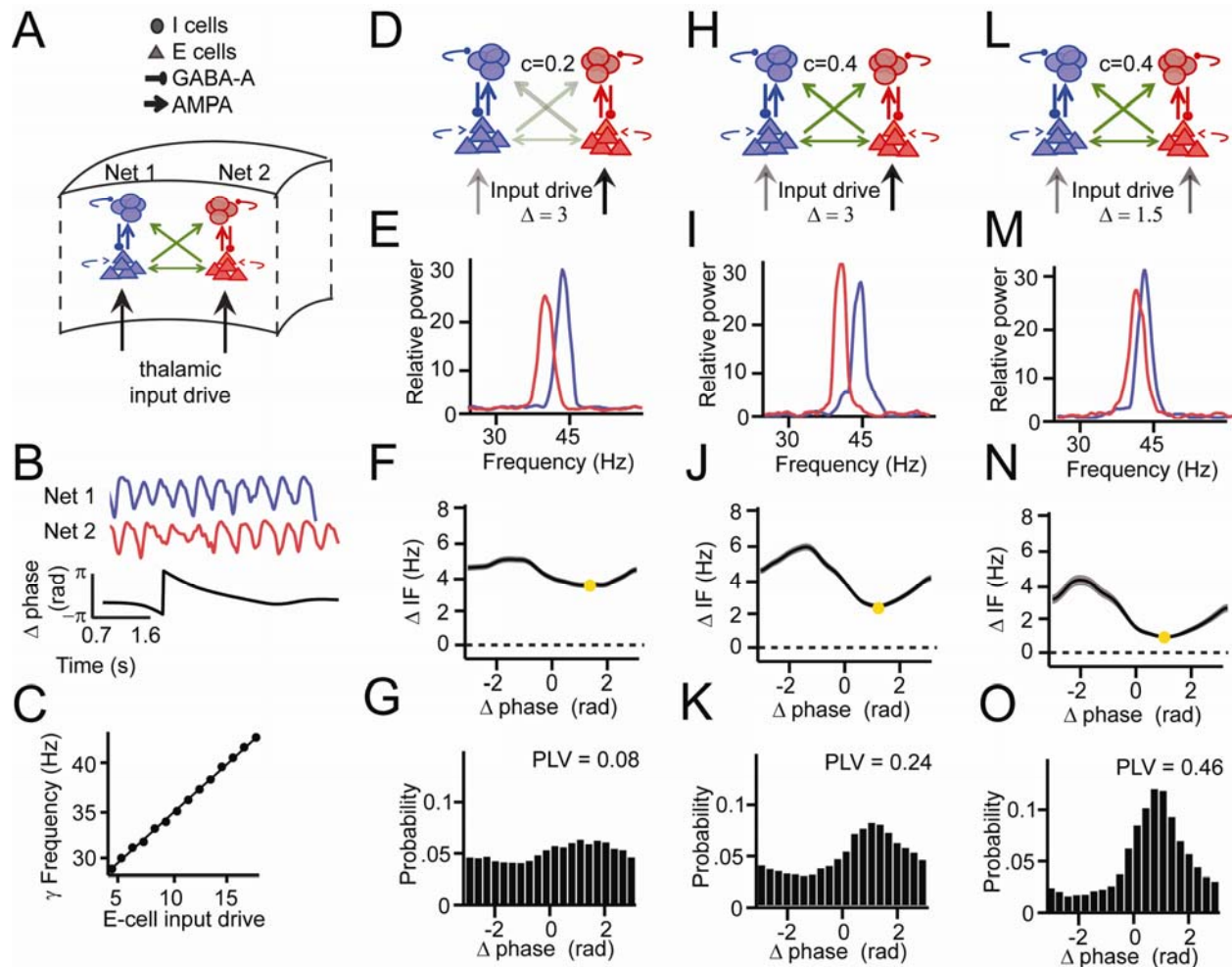


141  
 142 **Fig.1.** *Experimental paradigm and intermittent synchronization. (A) Recordings preparation and*  
 143 *example CSD (blue and red) traces from which phase difference (black) trace was extracted. The*  
 144 *gradient of the black trace indicates the rate of phase precession. (B) Spectral power relative to*  
 145 *baseline as a function of V1 cortical depth (36.5% contrast, population average, M1) dashed box*  
 146 *indicates gamma in the layers taken for main analysis (C) Local contrast modulated gamma*  
 147 *frequency (population average, M1). (D-G) Example 1 showing synchronization despite*  
 148 *frequency difference. (D) Section of the stimulus grating. Two receptive fields (RF) from different*  
 149 *probes are superimposed (blue and red circles). Below, black line gives contrast over space,*  
 150 *arrowheads mark RF positions. (E) Power spectra of the two probes showing different peak*  
 151 *frequencies. (F) Instantaneous frequency difference ( $\Delta IF$ ), equivalent to the phase precession*  
 152 *rate, as a function of phase difference. Yellow dot indicates the modulation minimum, equivalent*  
 153 *to the preferred phase difference, shading is  $\pm SE$  (G) The phase difference probability*  
 154 *distribution and phase-locking value (yellow dot, PLV). (H-K) Example 2; probes were closer,*  
 155 *gamma peak frequency difference was similar. Conventions as in D-G. (L-O) Example 3; same*  
 156 *distance, reduced frequency difference. Compare F, J, N; the RF distance determined IF*  
 157 *modulation amplitude, whereas contrast difference determined mean gamma frequency*  
 158 *difference*

159

160 **Experimental observations reproduced by two weakly coupled pyramidal-interneuron**  
161 **gamma (PING) networks**

162 To gain a first understanding of our experimental observations, we tested whether the findings  
163 were reproducible by a well-established biophysical model of cortical gamma rhythms (see  
164 Supplementary Information for more details). We simulated two coupled pyramidal-interneuron  
165 gamma (PING) networks (Fig.2A), which have been shown to capture many properties of  
166 cortical gamma rhythms (Börgers et al., 2005; Jadi and Sejnowski, 2014; Lowet et al., 2015;  
167 Tiesinga and Sejnowski, 2009, 2010). The network consisted of excitatory regular-spiking  
168 spiking neurons, representing pyramidal neurons, and fast-spiking inhibitory interneurons. We  
169 used the Izhikevich neural model (Izhikevich, 2003). Neurons were connected through excitatory  
170 AMPA and inhibitory GABA-A synapses. To mimic V1 horizontal connections (Stettler et al.,  
171 2002), the two PING networks were weakly coupled through excitatory cross-network  
172 connections that targeted the excitatory and inhibitory neurons of the receiving network. Each  
173 network received an independent source of excitatory drive, mimicking the effect of local visual  
174 contrast (Sclar et al., 1990). Neurons also received additional noise, such that the oscillation  
175 frequency was instable over time as observed for V1 gamma. For each network we estimated a  
176 population signal from which we extracted the instantaneous phase (Fig.2B). In line with our  
177 experimental observations and previous studies (Jia et al., 2013b; Lowet et al., 2015; Roberts et  
178 al., 2013; Tiesinga and Sejnowski, 2009), the input drive set the frequency of the gamma rhythm  
179 ( $R^2=0.98$ , Fig.2C). To reproduce the experimental V1 findings shown in Fig.1 (Fig.2D-O) we  
180 modulated the cross-network connection strength, mimicking cortical distance, and the  
181 difference of input drive between networks, mimicking the local contrast difference (Fig.2D, H,  
182 L). These manipulations led to effects on the spectra (Fig.2E,I,M), on the relationship of  
183 instantaneous frequency difference to phase difference (Fig.2F,J,N), and on phase-relation  
184 distributions (PLV and preferred phase difference) that were similar to those observed in the  
185 empirical V1 data. In particular, the modulation of the frequency difference between the gamma  
186 rhythms as a function of phase difference had an approximatively sinusoidal shape in the model  
187 data, as in the empirical V1 data. Stronger synchronization of gamma rhythms was associated  
188 with larger non-stationary modulations of the frequency difference. The strength of the  
189 modulation was changed by the synaptic connectivity between networks, whereas the input drive  
190 difference changed the frequency difference. As in V1, the phase difference probability  
191 distribution was determined by the frequency difference modulations: The mean frequency  
192 difference and the amplitude of the frequency modulation defined both the preferred phase-  
193 relation and the narrowness of the distribution (PLV). Taken together, this shows that the  
194 observations of V1 gamma can be accurately modelled by mutually interacting PING networks,  
195 in which synchronization is shaped by the phase-dependent instantaneous frequency  
196 modulations.



197

198 **Fig.2.** PING network simulations and intermittent synchronization. (A) Two coupled pyramidal-  
 199 interneuron gamma (PING) networks (Net 1 and Net 2). (B) Simulation output example network  
 200 signals (red and blue) and phase difference  $\theta$  (black) (C) The frequency of gamma in a single  
 201 network depends on input strength. (D-G) Example 1 showing synchronization despite frequency  
 202 difference. (D) Net 1 and Net 2 were relatively weakly coupled ( $c=0.2$ , where  $c$  defines max  
 203 synaptic connection strength of a uniform distribution  $[0, \max]$ ) and received a relatively large  
 204 input difference. (E) Power spectra of the two networks showed different peak frequencies. (F)  
 205 Instantaneous frequency difference ( $\Delta IF$ ), equivalent to phase precession rate, as a function of  
 206 phase difference. Yellow dot indicates the modulation minimum equivalent to the preferred phase  
 207 difference, shading is  $\pm SE$  (G) The phase difference probability distribution and phase-locking  
 208 value (PLV). (H-K) Example 2; networks were more strongly connected ( $c=0.4$ ), gamma peak  
 209 frequency difference was similar. Conventions as in D-G. (L-O) Example 3; same connection  
 210 strength, yet reduced frequency difference. Compare F, J, N; the connection strength determined  
 211 IF modulation amplitude, whereas input difference determined mean gamma frequency  
 212 difference.

213

214 **The theory of weakly coupled oscillators (TWCO): A framework for cortical gamma**  
215 **synchronization**

216 We now show how the observed synchronization behavior can be accounted for within the  
217 mathematical framework of the theory of weakly coupled oscillators (Ermentrout and Kleinfeld,  
218 2001; Hoppensteadt and Izhikevich, 1998; Kopell and Ermentrout, 2002; Kuramoto, 1991;  
219 Pikovsky et al., 2002; Winfree, 1967). Many oscillatory phenomena in the natural world  
220 represent dynamic systems with a limit-cycle attractor (Winfree, 2001). Although the underlying  
221 system might be complex (e.g. a neuron or neural population), the dynamics of the system can be  
222 reduced to a phase-variable if the interaction among oscillators is weak. If interaction strength is  
223 weak, amplitude changes are relatively small and play a minor role in the oscillatory dynamics.  
224 In this way, V1 neural populations can be approximated as oscillators, ‘weakly coupled’ by  
225 horizontal connections. The manner in which mutually coupled oscillators adjust their phases, by  
226 phase-delay and phase-advancement, is described by the phase response curve, the PRC (Brown  
227 et al., 2004; Canavier, 2015; Izhikevich, 2007; Kopell and Ermentrout, 2002; Schwemmer and  
228 Lewis, 2012). The PRC is important, because if the PRC of a system can be described, the  
229 synchronization behavior can be understood at a more general level and hence predicted across  
230 various conditions.

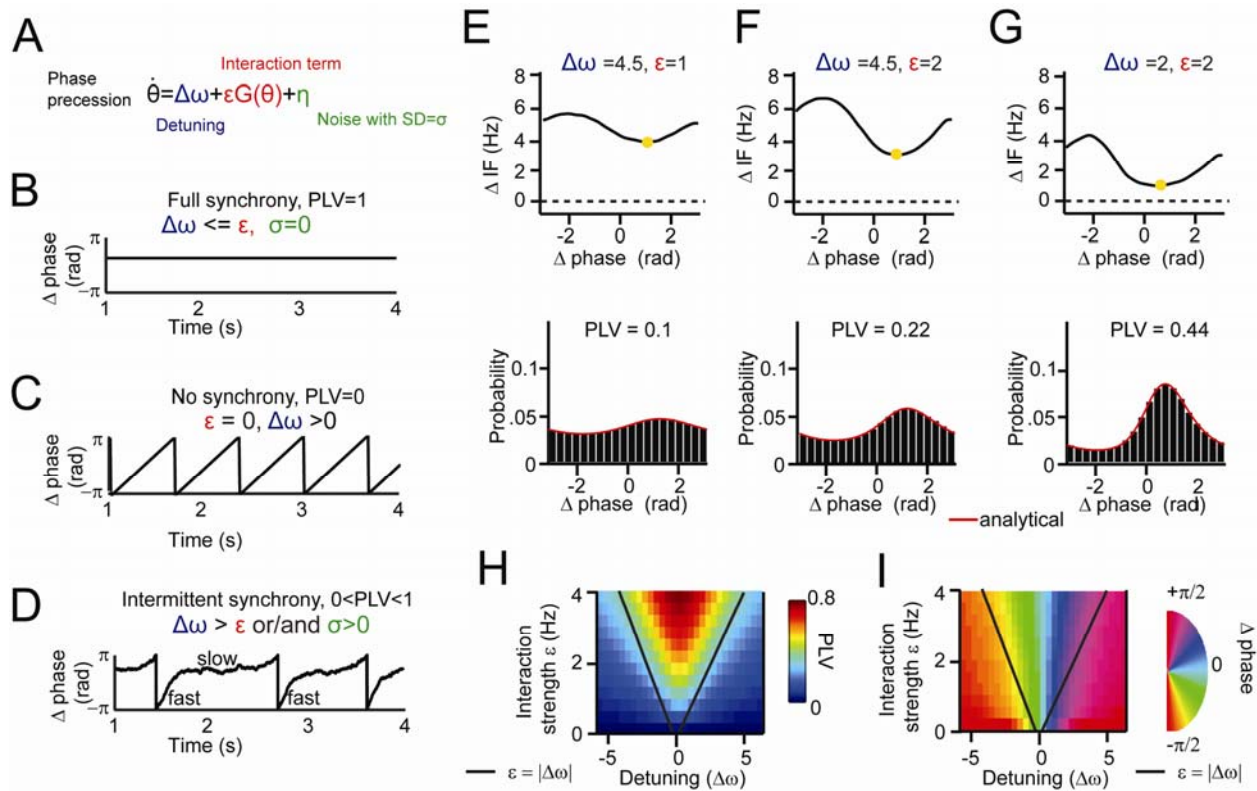
231 According to the theory, the synchronization of two coupled oscillators can be predicted from the  
232 forces they exert on each other as a function of their instantaneous phase difference. The amount  
233 of force is here defined as interaction strength and the interaction function as the PRC. Each  
234 oscillator has an intrinsic (natural) frequency and additionally an own source of phase noise,  
235 making the oscillators stochastic. The phase precession of two oscillators is given by (Fig.3A):

236 
$$(1) \dot{\theta} = \Delta\omega + \varepsilon G(\theta) + \eta$$

237 where  $\dot{\theta}$  is the time derivative of the phase difference  $\theta$  (the rate of phase precession),  $\Delta\omega$  the  
238 detuning (the intrinsic frequency difference),  $\varepsilon$  the interaction strength,  $G(\theta)$  is defined as the  
239 mutual PRC, and  $\eta$  the combined phase noise, where  $\eta \sim N(0, \sqrt{2\sigma^2})$ . Phase noise is defined here  
240 as variation, unrelated to interaction, that occurs for neural oscillators due to inherent instabilities  
241 of the generation mechanism (Atallah and Scanziani, 2009; Burns et al., 2010). This type of  
242 variation is distinct from measurement noise that is unrelated to the dynamics of the system. We  
243 express  $\omega$ ,  $\varepsilon$  and  $\eta$  in units of Hz (1Hz=2 $\pi$ \*rad/s). The time derivative  $\dot{\theta}$  is also expressed in Hz  
244 (instantaneous frequency, IF). The equation was solved analytically (see Supplementary  
245 Information) to study changes in the phase-difference probability distribution, here characterized  
246 by the PLV and the mean (preferred) phase difference, as a function of detuning  $\Delta\omega$  and  
247 interaction strength  $\varepsilon$ . The model’s behavior as a function of detuning  $\Delta\omega$  and interaction  
248 strength  $\varepsilon$  can be understood more easily by considering the noise-free case first. In the noise-  
249 free case ( $\sigma=0$ ) one can solve the equation for zero-points (equilibrium points), meaning that the  
250 phase precession is zero, ( $\dot{\theta} = 0$ , i.e. zero frequency difference). To reach equilibrium, the  
251 detuning  $\Delta\omega$  and the interaction term  $\varepsilon G(\theta)$  need to be counterbalanced. When detuning is



252 smaller than the interaction strength ( $\Delta\omega \leq \varepsilon$ ), then there is a particular phase difference  $\theta$  at  
 253 which an equilibrium can be reached. At equilibrium, there is no phase precession (Fig.3B) and  
 254 thus a PLV of 1 (full synchronization). When interaction strength is zero ( $\varepsilon=0$ ), the asynchronous  
 255 oscillators display continuous linear phase precession and have zero PLV (Fig.3C), with the  
 256 exception of zero detuning. When detuning is larger than a nonzero interaction strength ( $\Delta\omega > \varepsilon$ ,  
 257  $\varepsilon > 0$ ), oscillators exhibit a nonlinear phase precession over time, characteristic for the intermittent  
 258 synchronization regime (Izhikevich, 2007; Pikovsky et al., 2002, Fig.3D). The phase precession  
 259 rate (instantaneous frequency difference) is determined by the detuning  $\Delta\omega$ , the modulation  
 260 shape  $G(\theta)$ , and the modulation amplitude  $\varepsilon$ . Around the preferred phase-relation, the  
 261 instantaneous frequency difference is reduced ('slow' precession in Fig.3D), whereas away from  
 262 the preferred phase-relation, the instantaneous frequency is larger ('fast' precession in Fig.3D).  
 263 In this regime, PLV between 0 and 1 can be obtained. Including phase noise ( $\sigma > 0$ ) has important  
 264 effects on the synchronization behavior (Izhikevich, 2007; Pikovsky et al., 2002). The noise  
 265 flattens the phase-relation distribution and can induce full cycles of phase precession (phase  
 266 slips) that also lead to instantaneous frequency modulations. Hence, for noisy oscillators, the  
 267 intermittent synchronization regime is the default regime for a large parameter range.



268  
 269 **Fig.3.** Theory of weakly coupled oscillators (TWCO). (A) The single differential equation used  
 270 for analysis, with colors representing different key parameters. (B-D) Rate of phase precession  
 271 plotted in different synchronization regimes, with (B) full synchrony, (C) no synchrony and (D)  
 272 intermittent synchrony. For each plot, the corresponding range of the parameters and the PLV  
 273 are indicated. (E-G) Equivalent behavior as in the examples as Fig.1 and 2. Top is the

274 *modulation of the instantaneous frequency difference as a function of phase difference. Bottom is*  
275 *the phase difference probability distribution. Black bars are numerical simulation results,*  
276 *whereas the red line indicates the analytical solution. (E) Large detuning and low interaction*  
277 *strength. (F) Large detuning and strong interaction strength. (G) Small detuning and strong*  
278 *interaction strength. (H) The Arnold tongue. The analytically derived PLV is plotted as a*  
279 *function of interaction strength (y-axis) and detuning (x-axis). (I) The same as in (H), but for the*  
280 *mean (preferred) phase-relation. Black lines mark the predicted Arnold tongue borders in the*  
281 *noise-free case ( $\varepsilon=|\Delta\omega|$ ).*

282  
283 To show the applicability of the theory, we first reproduced the three examples shown in  
284 Fig.1 and 2 by numerical simulations of equation 1 and by varying detuning  $\Delta\omega$  and interaction  
285 strength  $\varepsilon$ . We assumed a sinusoidal  $G(\theta)$  (see Kuramoto model, Breakspear et al., 2010;  
286 Kuramoto, 1991) and a phase variability of  $SD=18\text{Hz}$ . As shown in Fig.3E-G, the same relation  
287 between the instantaneous frequency difference modulations and the properties of the phase  
288 difference probability distribution were observed as for V1 gamma data. Detuning defined the  
289 mean of the frequency modulations, whereas the interaction strength defined the amplitude of the  
290 modulations. To obtain a general description of the effect of detuning  $\Delta\omega$  and interaction strength  
291  $\varepsilon$ , we mapped the PLV and the mean phase difference (derived analytically) in the  $\Delta\omega$ - $\varepsilon$   
292 parameter space. We observed a triangular synchronization region (Fig.3H) described as the  
293 Arnold tongue (Pikovsky et al., 2002). This reflects the fact that stronger interaction strengths  
294 ‘tolerate’ larger detuning ( $\Delta\omega \leq \varepsilon$ ). Further, a clear phase gradient along the detuning dimension  
295 can be observed (Fig.3I). The oscillator with a higher frequency led the oscillator with a lower  
296 frequency in terms of their phases.

297

### 298 **Estimating the underlying parameters and function of TWCO in observed data**

299 To demonstrate the underlying principles of V1 gamma synchronization, we aimed to reconstruct  
300 its Arnold tongue, a central prediction of the theory. For comparison, we did the same for the  
301 coupled PING networks. Further, by estimating the parameters and function of equation 1, we  
302 aimed to directly test its accuracy by comparing analytical predictions to experimental  
303 observations in V1, and to simulation data from coupled PING networks.

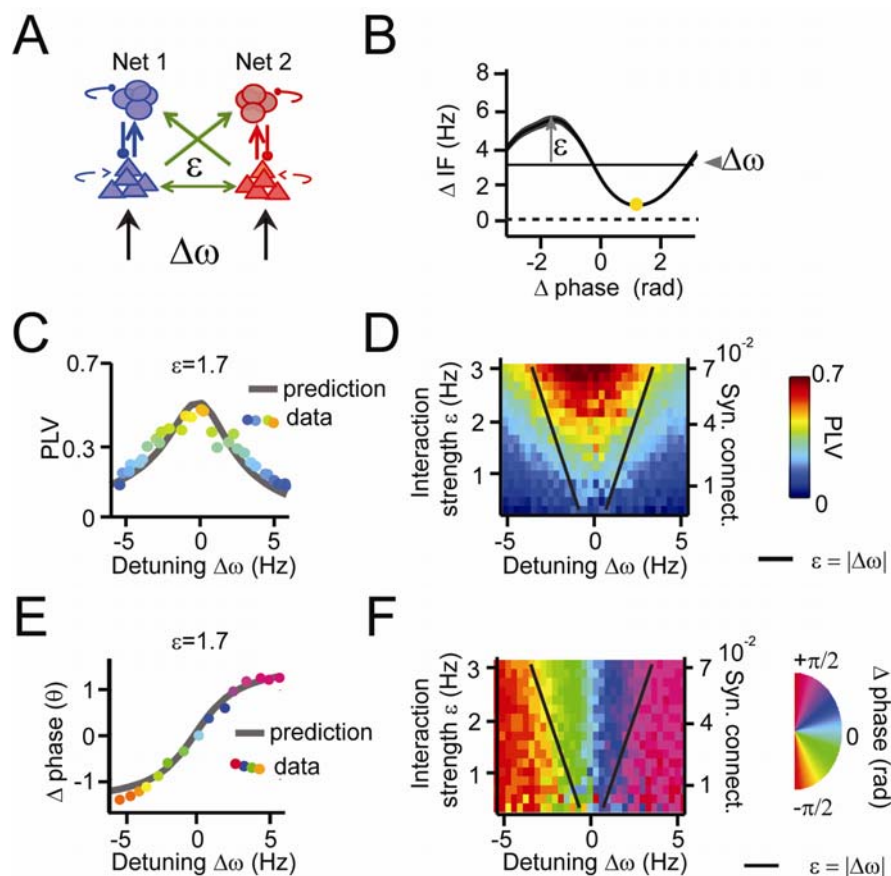
304 The theory predicts that the phase difference dependent modulations of instantaneous  
305 frequency difference ( $\Delta IF(\theta)$ ) are determined by the detuning  $\Delta\omega$  and the interaction term  $\varepsilon G(\theta)$ .  
306 In experimental data, we observed these systematic modulations. Thus, these modulations give  
307 information about the detuning and the properties of the interaction term. Specifically, the time-  
308 averaged modulation of the instantaneous frequency  $\Delta \overline{IF}(\theta)$  directly relates to the deterministic  
309 term  $\Delta\omega + \varepsilon G(\theta)$ , as noise is averaged out (see Supplementary Information). We estimated a  
310 single  $G(\theta)$  function (mutual PRC) and  $\sigma$  value for a given dataset (i.e. each monkey and the  
311 PING networks) assuming stability of underlying PRCs and of the noise sources, whereas  $\Delta\omega$   
312 and  $\varepsilon$  were estimated for each contact pair and condition.  $G(\theta)$  was estimated by the  $\Delta \overline{IF}(\theta)$

313 modulation shapes put to unity. The interaction strength  $\varepsilon$  was estimated by the modulation  
314 amplitude of the  $\Delta\overline{IF}(\theta)$ . The detuning  $\Delta\omega$  was estimated by the average value of the  $\Delta\overline{IF}(\theta)$   
315 computed over  $[-\pi, \pi]$ . The remaining parameter  $\sigma$  was approximated by finding the  $\sigma$  value for  
316 equation 1 that reproduced the observed overall instantaneous frequency variability (see  
317 supplementary materials). Given  $G(\theta)$  and the value  $\sigma$ , the equation can be mathematically  
318 (analytically) solved for any values of detuning  $\Delta\omega$  and interaction strength  $\varepsilon$ .

319

## 320 **TWCO predicts synchronization properties of weakly coupled PING networks**

321 We first tested the applicability of TWCO for the PING network simulation data. To test for the  
322 presence of the Arnold tongue in simulation data, we modulated detuning and interaction  
323 strength by varying input drive difference and cross-network connection strength respectively  
324 (Fig.4A). From the instantaneous frequency difference modulations (Fig.4B) we reconstructed  
325  $G(\theta)$ , which was approximately a sinusoidal function. This is noteworthy given that the  
326 excitatory cross-network connections mainly advanced the phase (Cannon and Kopell, 2015). As  
327 discussed later, this was because networks were mutually connected. Further, we estimated the  
328 remaining parameters: detuning, interaction strength and the phase noise variance ( $\sigma=15\text{Hz}$ ). Fig  
329 4C shows for an example level of interaction strength that the analytical predictions of PLV  
330 accurately predicted the simulated PLV (model accuracy:  $R^2=0.93$ ). Fig 4D demonstrates that  
331 mapping the gamma PLV in the  $\Delta\omega$  vs.  $\varepsilon$  parameter space yielded the Arnold tongue with a  
332 shape similar to the prediction by the TWCO. Likewise, Fig.4E shows the excellent match  
333 between analytical prediction and simulation data for the mean phase difference (model  
334 accuracy:  $R^2= 0.94$ ), and Fig.4F shows that the mean phase difference of simulated data in the  
335  $\Delta\omega - \varepsilon$  parameter space yielded the Arnold tongue (Fig.4E-F) with a shape similar to that  
336 predicted by the TWCO.



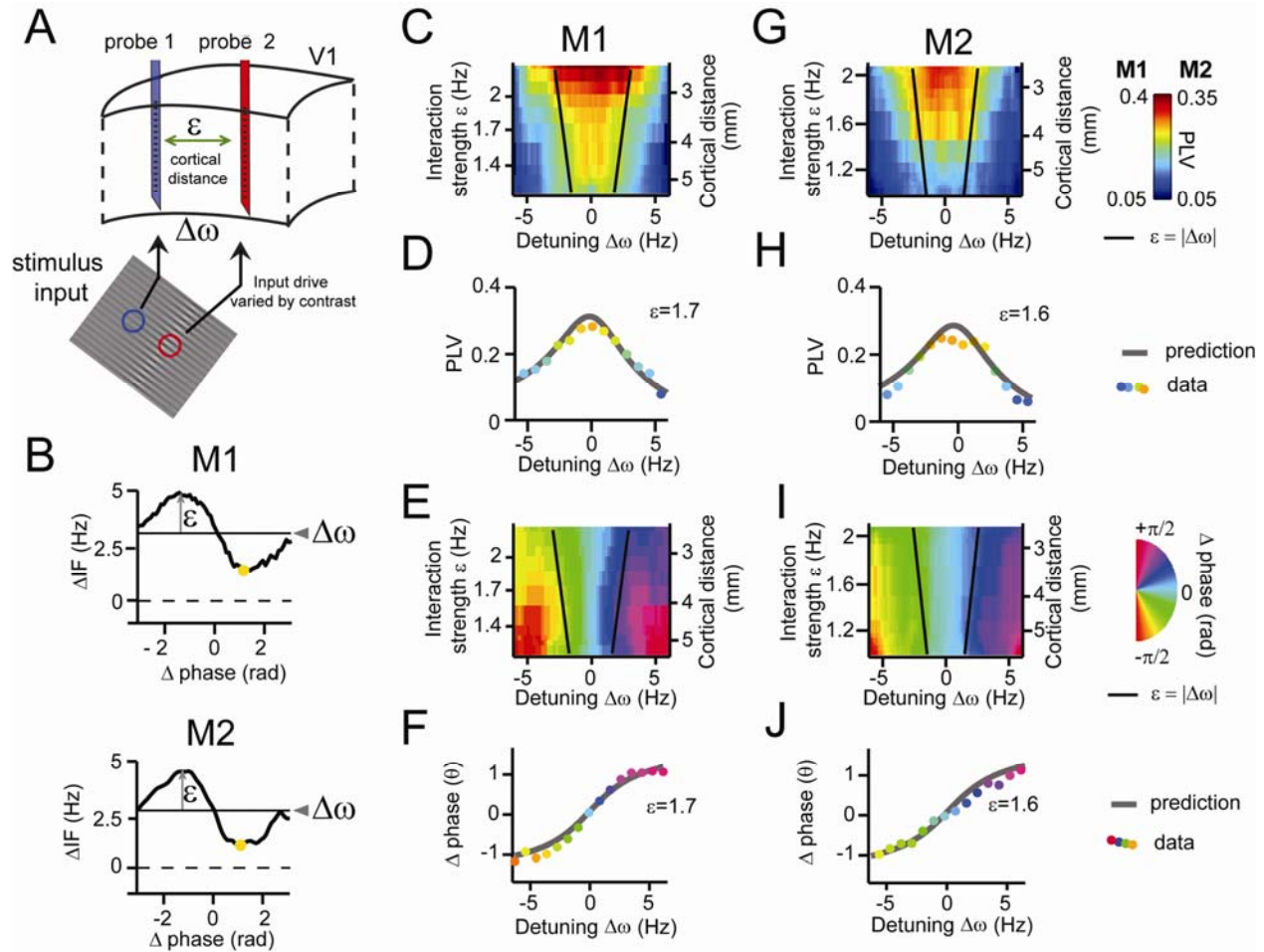
337  
 338 **Fig.4.** Applying the theory of weakly coupled oscillators to coupled PING networks. (A) Two  
 339 coupled pyramidal-interneuron gamma (PING) networks (Net 1 and Net 2). Detuning  $\Delta\omega$  was  
 340 varied by excitatory input drive, whereas interaction strength  $\varepsilon$  was varied by inter-network  
 341 connectivity strength. (B) An example plot of averaged phase-dependent modulation of the  
 342 instantaneous frequency difference ( $\Delta IF$ ) used for estimating  $\varepsilon$  and  $\Delta\omega$ . The shape of the  
 343 modulation indicates the  $G(\theta)$ . (C) The simulation PLV at different detuning values  $\Delta\omega$  (dots  
 344 colored by PLV) at a single interaction strength value ( $\varepsilon = 1.7$ ) was well predicted by the model  
 345 (gray line). (D) The PLV at many interaction strengths and detuning values mapped the Arnold  
 346 tongue. Black lines mark the predicted Arnold tongue borders in the noise-free case ( $\varepsilon = |\Delta\omega|$ ).  
 347 (E-F) As (F-G), but for preferred phase difference  $\theta$ .

348  
 349 **TWCO predicts synchronization properties of V1 cortical gamma rhythms**

350 We then tested whether the theory predicted the in vivo data with equal success. In the same  
 351 manner as with the PING modeling data, we estimated the underlying parameters using the  
 352 observed modulations of the instantaneous frequency difference (see  $\Delta \overline{IF}(\theta)$  examples in  
 353 Fig.5A,F), and the phase variance (M1: $\sigma=19$ Hz, M2: $\sigma=20$ Hz). The interaction strengths and  
 354 detuning values were estimated for each channel pair and condition separately.  $G(\theta)$  was again  
 355 approximately a sinusoidal function with symmetric negative and positive components (Akam et

356 al., 2012). The interaction strength  $\varepsilon$  was found to be inversely correlated with the cortical  
357 distance between probes (linear regression, M1:  $R^2=0.41$ , M2:  $R^2=0.29$ , both  $p < 10^{-10}$ ), in line  
358 with V1 horizontal connectivity (Stettler et al., 2002). The detuning  $\Delta\omega$  was correlated with the  
359 contrast difference between probes (linear regression, M1:  $R^2=0.31$ , M2:  $R^2=0.25$ , both  $p < 10^{-10}$ ,  
360 Fig.S2). Combining gamma PLV estimates from all recorded V1 pairs, we were able to reconstruct  
361 the Arnold tongue as a function of  $\Delta\omega$  and  $\varepsilon$  in both M1 and M2 (Fig.5C/G) confirming a central  
362 theoretical prediction. To better evaluate the accuracy of the theory, we derived analytical  
363 predictions for different  $\Delta\omega$  and  $\varepsilon$  by solving equation 1 using the estimated parameters. We  
364 found that the gamma PLV variation over all single contact pairs were substantially captured by  
365 the analytical predictions as a function of  $\Delta\omega$  and  $\varepsilon$  (model accuracy: M1:  $R^2=0.18$ ,  $n=7245$ , M2:  
366  $R^2=0.32$ ,  $n=7938$ ). The observed population means for different  $\Delta\omega$  and  $\varepsilon$  values followed the  
367 analytical predictions well (model accuracy: M1:  $R^2=0.83$ , M2:  $R^2=0.86$ , both  $n=638$ ). In  
368 Fig.5D/H we plotted a horizontal cross-section of the Arnold tongue that shows the good fit  
369 between the prediction and observed population means. The observation of a gamma Arnold  
370 tongue across the V1 middle-superficial layers was confirmed also for deep layer contacts  
371 (Fig.S4). We then mapped the mean phase difference (preferred phase-relation) between V1  
372 gamma rhythms as function of  $\Delta\omega$  and  $\varepsilon$ . We observed a clear phase gradient in both monkeys  
373 across the detuning dimension (Fig.5E/I). The phase spread (see also Fig.5F/J) had a range of  
374 nearly  $-\pi/2$  to  $\pi/2$  in both M1 and M2, as predicted by the shape of  $G(\theta)$ . Gamma rhythms with  
375 the higher frequency of a pair had the leading preferred phase relation. The mean phase  
376 difference increased with increased detuning. For given detuning, stronger interaction strength  
377 led to a reduction of the phase difference. Over all single contact pairs the mean phase difference  
378 was substantially captured by the analytical predictions (model accuracy: M1:  $R^2=0.56$ ,  $n=7245$ ,  
379 M2:  $R^2=0.3$ ,  $n=7938$ ). The observed population means for different  $\Delta\omega$  and  $\varepsilon$  values followed the  
380 analytical predictions precisely (model accuracy: M1:  $R^2=0.92$ , M2:  $R^2=0.88$ , both  $n=638$ ).

381 We confirmed the PLV and phase difference analysis in spike-CSD (spike-field) and  
382 spike-spike measurements (Fig.S5).



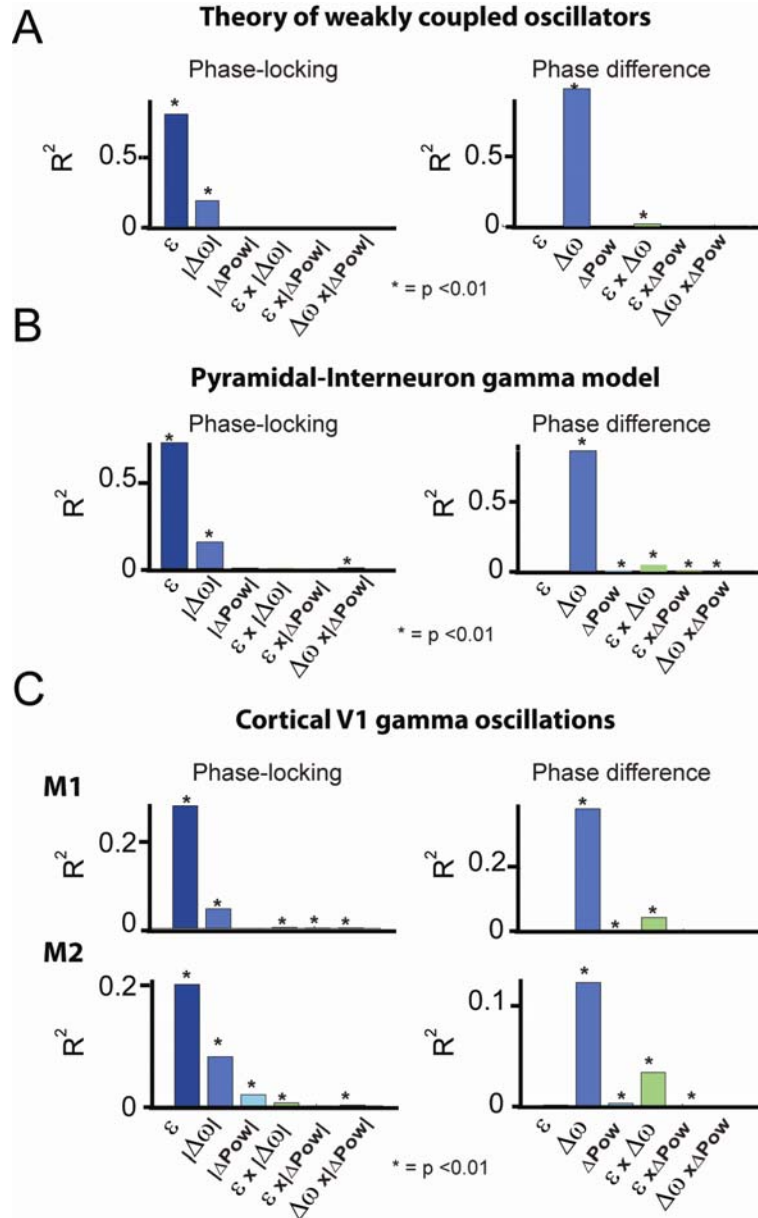
383  
 384 **Fig.5** Predicting V1 gamma synchronization. (A) Illustrative schema showing how detuning  $\Delta\omega$   
 385 and interaction strength  $\varepsilon$  of V1 gamma relate to local stimulus contrast and cortical distance  
 386 respectively. (B) An example plot of averaged phase-dependent modulation of the instantaneous  
 387 frequency difference ( $\Delta IF$ ) used for estimating  $\varepsilon$  and  $\Delta\omega$  for monkey M1 (top) and M2 (bottom).  
 388 The shape of the modulation indicates the  $G(\theta)$ . (C-F) Results from M1. (C) Observed PLV (dots)  
 389 and analytical prediction (gray line) as a function of detuning  $\Delta\omega$  for one level of interaction  
 390 strength ( $\varepsilon=1.7$ ). (D) Combining different detuning  $\Delta\omega$  and interaction strengths  $\varepsilon$  we observed a  
 391 triangular region of high synchronization, the Arnold tongue. Black lines mark the predicted  
 392 Arnold tongue border as expected from the noise-free case ( $\varepsilon=|\Delta\omega|$ ) (E) Analytical prediction  
 393 (gray) and experimentally observed preferred phase differences (dots colored by phase  
 394 difference) as a function of detuning  $\Delta\omega$  for one level of interaction strength ( $\varepsilon=1.7$ ). (F) Similar  
 395 to D), but now plotting the preferred phase difference. (G-J) As (C-F) but for M2 population  
 396 data. Color coding of dots in C, H, E, I is as indicated in color scales in panels just below them.

397

398

### 399 Comparison of TWCO, PING and V1 gamma synchronization

400 To reveal the individual contributions of detuning and interaction strength in regulating the PLV  
401 and the mean phase difference, we applied a multiple regression approach with detuning,  
402 interaction strength and amplitude as factors (Fig.6). The contributions were expressed in  
403 explained variance ( $R^2$ ). We found that the TWCO (Fig.6A) reflected the same pattern of  
404 contributions as we observed for PING (Fig.6B) and V1 gamma rhythms (Fig.6C). The phase  
405 locking value (PLV) was mainly determined by interaction strength and more weakly by  
406 detuning. The mean phase difference was however primarily determined by detuning and only  
407 weakly by interaction strength. Interaction strength affected the mean phase difference through  
408 an interaction effect with detuning by changing the detuning-to-phase-difference slope  
409 (interaction effect in Fig.6). In addition to the predictions of TWCO, we observed weak effects of  
410 the oscillation amplitude on the PLV and on the mean phase difference in PING and V1 gamma  
411 data. Amplitude differences between gamma rhythms can lead to asymmetric interaction  
412 strengths that shift the precise PLV and the preferred phase-relation. Further, in both PING and  
413 V1 data, we observed phase-dependent instantaneous amplitude modulations (Fig.S6). However,  
414 the analytical predictions and multiple regression analysis are in agreement in showing that  
415 detuning and interaction strength (frequency modulations) represent the main parameters for  
416 regulating V1 gamma synchronization.  
417



418  
 419 **Fig.6:** Multiple regression analysis of PLV and mean phase difference. (A) TWCO numerical  
 420 simulations ( $n=673$ ) including different detuning ( $-6\text{Hz}$  to  $6\text{Hz}$ ) and interaction strengths ( $0 < \varepsilon <$   
 421  $3.5$ ). (B) PING network simulations ( $n=697$ ) including different inter-network connection  
 422 strengths ( $0.008$ - $0.072$ ) and input drive differences ( $-5$  to  $5$ ). (C) Macaque V1 single contact  
 423 data including all contact pairs and conditions (M1:  $n=7245$ , M2:  $n=7938$ ). A significance value  
 424 below  $P < 0.01$  is marked with an asterisk. The results for PLV are on the left and for phase  
 425 difference are on the right. Contributions are expressed in explained variance ( $R^2$ ).

426  
 427  
 428  
 429



## 430 **DISCUSSION**

431 The present study shows that gamma synchronization in awake monkey V1 adheres to  
432 theoretical principles of weakly coupled oscillators (Ermentrout and Kleinfeld, 2001;  
433 Hoppensteadt and Izhikevich, 1998; Kopell and Ermentrout, 2002; Kuramoto, 1991; Pikovsky et  
434 al., 2002; Winfree, 1967), thereby providing insight into the synchronization regime of gamma  
435 rhythms and its principles. Given the generality of the synchronization principles, they are likely  
436 to apply to other brain regions and frequency bands.

437

### 438 **Intermittent synchronization: The role of non-stationary frequency modulations**

439 Our findings reveal the importance of phase-dependent frequency modulations for synchronizing  
440 V1 gamma rhythms. The same modulations were observed in a general biophysical model of  
441 gamma rhythms. These modulations show that a fixed and common frequency is not required for  
442 phase coordination. To the contrary, stronger non-stationary frequency modulations led to  
443 stronger synchronization, and thus to more reliable phase coordination. These modulations arise  
444 naturally in the intermittent synchronization regime (Izhikevich, 2007; Pikovsky et al., 2002),  
445 when oscillators cannot remain in a stable equilibrium due to detuning and noise. Given the  
446 variable nature of gamma rhythms in vivo (Atallah and Scanziani, 2009; Burns et al., 2010; Ray  
447 and Maunsell, 2010; Roberts et al., 2013), intermittent synchronization is the most likely regime  
448 for their phase coordination. Although complete synchronization is not achieved in this regime,  
449 phase coordination remains sufficiently robust to influence the strength and directionality of  
450 information flow (Battaglia et al., 2012; Buehlmann and Deco, 2010; Fries, 2015; Maris et al.,  
451 2016), by rendering particular phase-relations more likely than others. The observation of non-  
452 stationary frequency modulations also has methodological implications. Gamma rhythms are  
453 often studied with stationary methods, for example spectral coherence or stationary granger  
454 measures, yet our findings are not in line with the (weak-sense) stationarity assumption (Lachaux  
455 et al., 1999; Lowet et al., 2016). Time-resolved non-stationary methods are therefore more  
456 appropriate to study the dynamics underling gamma synchronization.

457

### 458 **The interaction function of V1 gamma rhythms**

459 We show that the shape of the frequency modulations reflects the underlying interaction  
460 function, the PRC (Hoppensteadt and Izhikevich, 1998; Kopell and Ermentrout, 2002;  
461 Kuramoto, 1991; Pikovsky et al., 2002; Winfree, 1967). The PRC defines how the oscillators  
462 advance or delay each other's phase development to coordinate their phase-relation. We  
463 observed symmetric sinusoidal-like functions in both PING and in V1 gamma that resemble the  
464 basic function of the widely-used Kuramoto-model (Breakspear et al., 2010). This is in  
465 agreement with the biphasic PRC of gamma rhythms observed in the rat hippocampus (Akam et  
466 al., 2012). In agreement with our symmetric  $G(\theta)$ , we observed symmetric Arnold tongues  
467 (Izhikevich, 2007; Kopell and Ermentrout, 2002; Pikovsky et al., 2002). Importantly, here we  
468 estimated the mutual (bidirectional) PRC, the  $G(\theta)$ . This function can be symmetric (equal  
469 magnitude of phase advance and delay), despite asymmetric individual (unidirectional) PRCs, as

470 long as the rhythms interact approximatively equally strongly, which is a plausible assumption  
471 between V1 locations. Therefore, our results are not per se at odds with other studies that have  
472 indicated asymmetric individual PRC in neural data (Cannon and Kopell, 2015; Wang et al.,  
473 2013). Unidirectionally connected neural groups, for example between certain cortical areas,  
474 might have asymmetric PRC and hence an asymmetric Arnold tongue. In this situation a  
475 frequency difference between cortical areas (Bosman et al., 2012; Cannon et al., 2014) might be  
476 favorable for optimal information transmission. This hypothesis could be tested between gamma  
477 rhythms recorded from unidirectionally connected cortical areas.

478

### 479 **The Arnold tongue and the regulative parameters of gamma synchronization**

480 Previous studies have established diversity in the phase-locking (Eckhorn et al., 2001; Gray and  
481 Singer, 1989; Ray and Maunsell, 2010) and in the phase-relation (Maris et al., 2016; Vinck et al.,  
482 2010) of gamma rhythms in the primate visual cortex. However, how this diversity is regulated  
483 was not well established. Here, we show that two parameters mainly determined gamma  
484 synchronization: the detuning (frequency difference) and the interaction strength  $\varepsilon$  (frequency  
485 modulations). This was highlighted in the mapping of the Arnold tongue, offering a graphical  
486 understanding of how these parameters shape gamma-band synchronization. Detuning represents  
487 a desynchronization force, whereas the interaction strength represents a synchronization force.  
488 The former was modulated by input drive differences, and the latter by connectivity strength.  
489 Their interplay defined the resultant phase-locking strength and the preferred phase-relation  
490 between gamma rhythms. The observed role of detuning is in agreement with a previous study in  
491 the rat hippocampus (Akam et al., 2012), in which optogenetic entrainment strength and phase of  
492 gamma rhythms were dependent on the frequency-detuning. The results also agree with  
493 theoretical conceptions on oscillatory interactions (Ermentrout and Kopell, 1984; Hoppensteadt  
494 and Izhikevich, 1998; Sancristóbal et al., 2014; Tiesinga and Sejnowski, 2010). We suggest that  
495 small detuning values (mainly  $<\Delta 10\text{Hz}$ ) reported in the present study and much larger shifts in  
496 the gamma frequency-range (25-50Hz to 65-120Hz) reported in the rat hippocampus and cortex  
497 (Colgin et al., 2009) represent different but complementary mechanisms for controlling gamma  
498 synchronization. In this perspective, large shifts in the frequency-range could selectively turn on  
499 or off gamma-mediated information flow between brain regions, whereas fine frequency  
500 detuning modulates the exact strength and direction of the gamma-mediated information flow.  
501 The role of instantaneous frequency modulations, defining the interaction strength, reflects the  
502 overall ability of two cortical locations to engage in gamma-band synchronization. These  
503 modulations are mediated by anatomical connectivity and further modified by oscillation  
504 amplitude. Hence, an important source of instantaneous V1 gamma frequency modulations  
505 (Bosman et al., 2009; Burns et al., 2011, 2010; Roberts et al., 2013) is the underlying network  
506 (intermittent) synchronization process. Instantaneous gamma frequency fluctuations have also  
507 been observed in the rat hippocampus by Atallah and Scanziani (2009). Their data suggested that  
508 these fluctuations, which reflected rapid phase shifts due to changes in excitation-inhibition  
509 balance, might be critical for gamma-mediated information flow. In line with this notion, we

510 show that these cycle-by-cycle modulations are essential for regulating synchronization  
511 properties between gamma rhythms.

512

### 513 **Role of V1 gamma synchronization for visual processing**

514 In our experiment, detuning was dependent on the local contrast difference (Ray and Maunsell,  
515 2010; Roberts et al., 2013), known to change neural excitation in V1 (Sclar et al., 1990), while  
516 the interaction strength was dependent on the underlying horizontal connectivity strength, here  
517 varied by cortical distance (Stettler et al., 2002). Gamma synchronization is therefore  
518 informative about the sensory input (Besserve et al., 2015) and informative about the underlying  
519 structure of connectivity. Indeed, the frequency of gamma rhythms is modulated by various  
520 sensory stimuli (Fries, 2015) and by cognitive manipulations (Bosman et al., 2012; Buzsáki and  
521 Wang, 2012; Fries, 2015) suggesting that frequency control is critical for functional V1 gamma-  
522 band coordination. The horizontal connectivity in V1 is not only local, but also exhibits  
523 remarkable tuning to visual features, orientation being a prime example (Stettler et al., 2002).  
524 Hence, innate and learned connectivity patterns likely affect the interaction strength and hence  
525 the synchronization patterns of gamma rhythms within V1. These properties suggest V1 gamma  
526 as a functional mechanism for early vision (Eckhorn et al., 2001; Gray and Singer, 1989) by  
527 temporally coordinating local neural activity as a function of sensory input and connectivity.  
528 However, in line with previous studies (Eckhorn et al., 2001; Palanca and DeAngelis, 2005), V1  
529 gamma synchronization was found to be mainly local and hence not likely to ‘bind’ whole  
530 perceptual objects. Furthermore, recent studies on the gamma-band response during natural  
531 viewing (Brunet et al., 2013; Hermes et al., 2014) have found variable levels of synchronization  
532 power for different natural images. In line with these observations, the revealed Arnold tongue of  
533 V1 gamma implies that natural image parts with high input/detuning variability (heterogeneity)  
534 will induce no or weak synchronization, whereas parts with low input/detuning variability  
535 (homogeneity) will induce strong synchronization. This is also in line with proposals linking  
536 gamma synchronization with surround suppression/normalization (Gieselmann and Thiele, 2008;  
537 Ray et al., 2013) and predictive coding (Vinck and Bosman, 2016). Our findings and  
538 interpretation shed new light onto the operation of gamma synchronization in the brain and will  
539 permit new and more detailed description of the mechanisms by which synchronization is  
540 regulated by cognitive and sensory inputs.

541

### 542 **Experimental Procedures:**

#### 543 Species used and surgical procedures

544 Two adult male rhesus monkeys were used in this study. A chamber was implanted above early  
545 visual cortex, positioned over V1/V2. A head post was implanted to head-fix the monkeys during  
546 the experiment. All the procedures were in accordance with the European council directive  
547 2010/63/EU, the Dutch ‘experiments on animal acts’ (1997) and approved by the Radboud  
548 University ethical committee on experiments with animals (Dier-Experimenten-Commissie,  
549 DEC).

550

### 551 Recording methods

552 V1 recordings were made with 2 or 3 Plexon U-probes (Plexon Inc.) consisting of 16 contacts  
553 (150 $\mu$ m inter-contact spacing). We recorded the local field potential (LFP) and multi-unit  
554 spiking activity (MUA). For the main analysis we used the current-source density (CSD, (Vaknin  
555 et al., 1988)) to reduce volume conduction. We aligned the neural data from the different laminar  
556 probes according to their cortical depth and excluded contacts coming from deep V2. Layer  
557 assignment was based on the stimulus-onset CSD profile (Schroeder et al., 1991) and the inter-  
558 laminar coherence pattern (Maier et al., 2010). Receptive field (RF) mapping was achieved by  
559 presenting at fast rate high-contrast black and white squares pseudorandomly on a 10x10 grid  
560 (Roberts et al., 2013). For RF mapping we used CSD signals and spikes.

561

### 562 Task and visual stimuli

563 The monkeys were trained for head-fixation and were placed in a Faraday-isolated darkened  
564 booth at a distance of 57cm from a computer screen. Stimuli were presented on a Samsung TFT  
565 screen (SyncMaster 940bf, 38 $^{\circ}$ x30 $^{\circ}$  60Hz). During stimulation and pre-stimulus time the monkey  
566 maintained a central eye position (measured by infra-red camera, Arrington, 60Hz sampling  
567 rate). The monkey's task was to passively gaze on a fixation point while a stimulus was shown.  
568 The monkey was rewarded for correct trials. The local stimulus contrast was manipulated in a  
569 whole-field static square-wave grating (2 cycles/degree, presented at two opposite phases  
570 randomly interleaved). Contrast was varied smoothly over space such that different RFs had  
571 different contrast values. The direction of the contrast difference was parallel to the arrangement  
572 of RFs and orthogonal to the orientation of the grating. The stimulus was isoluminant at all  
573 points and was isoluminant with the pre-stimulus grey screen. We presented 9 different contrast  
574 modulation conditions (Table.S1). Cortex software (<http://dally.nimh.nih.gov/index.html>) was  
575 used for visual stimulation and behavioral control.

576

### 577 Data analysis

578 To investigate dynamical changes in the gamma phase and frequency over time we estimated the  
579 instantaneous gamma phase and frequency using the singular spectrum decomposition of the  
580 signal (SSD (Bonizzi et al., 2014), see <https://project.dke.maastrichtuniversity.nl/ssd/>) combined  
581 with Hilbert-Transform or wavelet-decomposition. The phase-locking value (PLV) was  
582 estimated as the mean resultant vector length (Lachaux et al., 1999) and the preferred phase-  
583 relation as the mean resultant vector angle. For experimental data, we estimated the signal-to-  
584 noise ratio (SNR) to reduce the influence of measurement noise on estimates. Phase flipping due  
585 to CSD computation was corrected.

586

### 587 Theoretical and computational modelling

588 Using the theory of weakly coupled oscillators we investigated the phase-locking as well as the  
589 mean phase difference of two mutually coupled noisy phase-oscillators with variable frequency

590 difference (detuning) and interaction strength. The stochastic differential equation was solved  
591 analytically (Pikovsky et al., 2002). The analytical results correctly predicted the numerical  
592 simulations. In addition, we simulated two coupled excitatory-inhibitory spiking networks  
593 generating gamma oscillations using the Izhikevich-type neuronal model (Izhikevich, 2003). The  
594 detuning between the networks was altered by changing the difference in excitatory input drive.  
595 The interaction strength was altered by changing the cross-network synaptic connection strength.

596

### 597 Statistics

598 The accuracy of the theoretical predictions for the experimental data was quantified as the  
599 explained variance  $R^2$ . In addition, to evaluate the contribution of different parameters we used a  
600 multiple regression approach (Matlab function fitlm, The MathWorks Inc.).

601

602 **Author contributions:** E.L., M.J.R. and P.DW. designed the experiment. E.L. and M.J.R.  
603 conducted the recordings. Data analysis and the writing of the manuscript was by E.L. with  
604 support by M.J.R., A.P., B.G. and P.DW.

605

606 **Acknowledgments:** We thank N.Kopell, W.Singer, A.Bastos, P.Fries, C.Micheli, F.Smolders,  
607 J.v.d.Eerden, J.Karel, P.Bonizzi, A.Hadjipapas, A.A.v.d.Berg. Supported by NWO VICI grant  
608 453-04-002 to PDW and NWO VENI grant 451-09-025 to MJR. All data are stored at the  
609 Department of Psychology and Neuroscience, Maastricht University, The Netherlands. We thank  
610 the Radboud University Nijmegen for hosting our experiments, and staff of the Central Animal  
611 Facility (CDL) for expert assistance.

612

### 613 **REFERENCES:**

- 614 Akam, T., Oren, I., Mantoan, L., Ferenczi, E., Kullmann, D., 2012. Oscillatory dynamics in the  
615 hippocampus support dentate gyrus–CA3 coupling. *Nat. Neurosci.* 1–9.  
616 doi:10.1038/nn.3081
- 617 Atallah, B. V., Scanziani, M., 2009. Instantaneous modulation of gamma oscillation frequency by  
618 balancing excitation with inhibition. *Neuron* 62, 566–577.  
619 doi:10.1016/j.neuron.2009.04.027
- 620 Bartos, M., Vida, I., Jonas, P., 2007. Synaptic mechanisms of synchronized gamma oscillations  
621 in inhibitory interneuron networks. *Nat. Rev. Neurosci.* 8, 45–56. doi:10.1038/nrn2044
- 622 Battaglia, D., Witt, A., Wolf, F., Geisel, T., 2012. Dynamic effective connectivity of inter-areal  
623 brain circuits. *PLoS Comput Biol* 8, e1002438. doi:10.1371/journal.pcbi.1002438
- 624 Besserve, M., Lowe, S.C., Logothetis, N.K., Schoelkopf, B., Panzeri, S., 2015. Shifts of Gamma  
625 Phase across Primary Visual Cortical Sites Reflect Dynamic Stimulus-Modulated  
626 Information Transfer. *PLoS Biol.* 13.
- 627 Bonizzi, P., Karel, J.M.H., Meste, O., Peeters, R.L.M., 2014. Singular spectrum decomposition:  
628 A new method for time series decomposition. *Adv. Adapt. Data Anal.* 1450011.  
629 doi:10.1142/S1793536914500113
- 630 Börgers, C., Epstein, S., Kopell, N.J., 2005. Background gamma rhythmicity and attention in  
631 cortical local circuits: a computational study. *Proc. Natl. Acad. Sci. U. S. A.* 102, 7002–7.

- 632 doi:10.1073/pnas.0502366102
- 633 Bosman, C.A., Schoffelen, J.-M., Brunet, N., Oostenveld, R., Bastos, A.M., Womelsdorf, T.,  
634 Rubehn, B., Stieglitz, T., De Weerd, P., Fries, P., 2012. Attentional stimulus selection  
635 through selective synchronization between monkey visual areas. *Neuron* 75, 875–888.  
636 doi:10.1016/j.neuron.2012.06.037
- 637 Bosman, C.A., Womelsdorf, T., Desimone, R., Fries, P., 2009. A microsaccadic rhythm  
638 modulates gamma-band synchronization and behavior. *J Neurosci* 29, 9471–9480.  
639 doi:10.1523/JNEUROSCI.1193-09.2009
- 640 Breakspear, M., Heitmann, S., Daffertshofer, A., 2010. Generative models of cortical  
641 oscillations: neurobiological implications of the kuramoto model. *Front Hum Neurosci* 4,  
642 190. doi:10.3389/fnhum.2010.00190
- 643 Brown, E., Moehlis, J., Holmes, P., 2004. On the phase reduction and response dynamics of  
644 neural oscillator populations. *Neural Comput.* 16, 673–715.  
645 doi:10.1162/089976604322860668
- 646 Brunet, N., Bosman, C. a, Roberts, M., Oostenveld, R., Womelsdorf, T., De Weerd, P., Fries, P.,  
647 2013. Visual Cortical Gamma-Band Activity During Free Viewing of Natural Images.  
648 *Cereb. Cortex* 25, 1–9. doi:10.1093/cercor/bht280
- 649 Buehlmann, A., Deco, G., 2010. Optimal information transfer in the cortex through  
650 synchronization. *PLoS Comput. Biol.* 6. doi:10.1371/journal.pcbi.1000934
- 651 Burns, S.P., Xing, D., Shapley, R.M., 2011. Is gamma-band activity in the local field potential of  
652 V1 cortex a “clock” or filtered noise? *J Neurosci* 31, 9658–9664.  
653 doi:10.1523/JNEUROSCI.0660-11.2011
- 654 Burns, S.P., Xing, D., Shelley, M.J., Shapley, R.M., 2010. Searching for autocoherece in the  
655 cortical network with a time-frequency analysis of the local field potential. *J Neurosci* 30,  
656 4033–4047. doi:10.1523/JNEUROSCI.5319-09.2010
- 657 Buzsáki, G., Wang, X.-J., 2012. Mechanisms of gamma oscillations. *Annu Rev Neurosci* 35,  
658 203–225. doi:10.1146/annurev-neuro-062111-150444
- 659 Canavier, C.C., 2015. Phase-resetting as a tool of information transmission. *Curr. Opin.*  
660 *Neurobiol.* doi:10.1016/j.conb.2014.12.003
- 661 Cannon, J., Kopell, N., 2015. The Leaky Oscillator: Properties of Inhibition-Based Rhythms  
662 Revealed through the Singular Phase Response Curve. *SIAM J. Appl. Dyn. Syst.* 14, 1930–  
663 1977. doi:10.1137/140977151
- 664 Cannon, J., McCarthy, M.M., Lee, S., Lee, J., Börgers, C., Whittington, M.A., Kopell, N., 2014.  
665 Neurosystems: brain rhythms and cognitive processing. *Eur. J. Neurosci.* 39, 705–19.  
666 doi:10.1111/ejn.12453
- 667 Cardin, J.A., Carlén, M., Meletis, K., Knoblich, U., Zhang, F., Deisseroth, K., Tsai, L.-H.,  
668 Moore, C.I., 2009. Driving fast-spiking cells induces gamma rhythm and controls sensory  
669 responses. *Nature* 459, 663–667. doi:10.1038/nature08002
- 670 Carter, G., Knapp, C., Nuttall, A., 1973. Estimation of the magnitude-squared coherence function  
671 via overlapped fast Fourier transform processing. *IEEE Trans. Audio Electroacoust.* 21.  
672 doi:10.1109/TAU.1973.1162496
- 673 Chalk, M., Gutkin, B., Deneve, S., 2015. Neural oscillations as a signature of efficient coding in  
674 the presence of synaptic delays, bioRxiv. Cold Spring Harbor Labs Journals.  
675 doi:10.1101/034736
- 676 Colgin, L.L., Denninger, T., Fyhn, M., Hafting, T., Bonnevie, T., Jensen, O., Moser, M.-B.,  
677 Moser, E.I., 2009. Frequency of gamma oscillations routes flow of information in the

- 678 hippocampus. *Nature* 462, 353–357. doi:10.1038/nature08573
- 679 Eckhorn, R., Bruns, A., Saam, M., Gail, A., Gabriel, A., Brinksmeier, H.J., 2001. Flexible  
680 cortical gamma-band correlations suggest neural principles of visual processing. *Vis. cogn.*  
681 8, 519–530. doi:10.1080/13506280143000098
- 682 Engel, A.K., Fries, P., König, P., Brecht, M., Singer, W., 1999. Temporal binding, binocular  
683 rivalry, and consciousness. *Conscious. Cogn.* 8, 128–51. doi:10.1006/ccog.1999.0389
- 684 Ermentrout, G.B., Kleinfeld, D., 2001. Traveling electrical waves in cortex: insights from phase  
685 dynamics and speculation on a computational role. *Neuron* 29, 33–44.
- 686 Ermentrout, G.B., Kopell, N., 1984. Frequency Plateaus in a Chain of Weakly Coupled  
687 Oscillators, I. *SIAM J. Math. Anal.* 15, 215–237. doi:10.1137/0515019
- 688 Fries, P., 2015. Rhythms For Cognition: Communication Through Coherence. *Neuron*.
- 689 Fries, P., Neuenschwander, S., Engel, a K., Goebel, R., Singer, W., 2001. Rapid feature  
690 selective neuronal synchronization through correlated latency shifting. *Nat. Neurosci.* 4,  
691 194–200. doi:10.1038/84032
- 692 Gail, A., Brinksmeier, H.J., Eckhorn, R., 2000. Contour decouples gamma activity across  
693 texture representation in monkey striate cortex. *Cereb Cortex* 10, 840–850.
- 694 Gieselmann, M.A., Thiele, A., 2008. Comparison of spatial integration and surround suppression  
695 characteristics in spiking activity and the local field potential in macaque V1. *Eur J*  
696 *Neurosci* 28, 447–459. doi:10.1111/j.1460-9568.2008.06358.x
- 697 Gray, C.M., Singer, W., 1989. Stimulus-specific neuronal oscillations in orientation columns of  
698 cat visual cortex. *Proc. Natl. Acad. Sci. U. S. A.* 86, 1698–702.
- 699 Gregoriou, G.G., Gotts, S.J., Zhou, H., Desimone, R., 2009. High-frequency, long-range  
700 coupling between prefrontal and visual cortex during attention. *Science* 324, 1207–1210.  
701 doi:10.1126/science.1171402
- 702 Grothe, I., Neitzel, S.D., Mandon, S., Kreiter, A.K., 2012. Switching neuronal inputs by  
703 differential modulations of gamma-band phase-coherence. *J. Neurosci.* 32, 16172–80.  
704 doi:10.1523/JNEUROSCI.0890-12.2012
- 705 Havenith, M.N., Yu, S., Biederlack, J., Chen, N.-H., Singer, W., Nikolić, D., 2011. Synchrony  
706 makes neurons fire in sequence, and stimulus properties determine who is ahead. *J.*  
707 *Neurosci.* 31, 8570–84. doi:10.1523/JNEUROSCI.2817-10.2011
- 708 Hermes, D., Miller, K.J., Wandell, B. a, Winawer, J., 2014. Stimulus Dependence of Gamma  
709 Oscillations in Human Visual Cortex. *Cereb. Cortex* 1–9. doi:10.1093/cercor/bhu091
- 710 Hoppensteadt, F.C., Izhikevich, E.M., 1998. Thalamo-cortical interactions modeled by weakly  
711 connected oscillators: could the brain use FM radio principles? *Biosystems* 48, 85–94.
- 712 Izhikevich, E., Kuramoto, Y., 2006. Weakly coupled oscillators. *Encycl. Math. Phys.* 48–53.
- 713 Izhikevich, E.M., 2003. Simple model of spiking neurons. *IEEE Trans Neural Netw* 14, 1569–  
714 1572. doi:10.1109/TNN.2003.820440
- 715 Izhikevich, E.M., 2007. *Dynamical Systems in Neuroscience: The Geometry of Excitability and*  
716 *Bursting, Dynamical Systems.* doi:10.1017/S0143385704000173
- 717 Jadi, M.P., Sejnowski, T.J., 2014. Cortical oscillations arise from contextual interactions that  
718 regulate sparse coding. *Proc. Natl. Acad. Sci. U. S. A.* 111, 6780–5.  
719 doi:10.1073/pnas.1405300111
- 720 Jensen, O., Gips, B., Bergmann, T.O., Bonnefond, M., 2014. Temporal coding organized by  
721 coupled alpha and gamma oscillations prioritize visual processing. *Trends Neurosci.* 37,  
722 357–369. doi:10.1016/j.tins.2014.04.001
- 723 Jia, X., Tanabe, S., Kohn, A., 2013a.  $\gamma$  and the coordination of spiking activity in early visual

- 724 cortex. *Neuron* 77, 762–74. doi:10.1016/j.neuron.2012.12.036
- 725 Jia, X., Xing, D., Kohn, A., 2013b. No consistent relationship between gamma power and peak  
726 frequency in macaque primary visual cortex. *J Neurosci* 33, 17–25.  
727 doi:10.1523/JNEUROSCI.1687-12.2013
- 728 Kopell, N., Ermentrout, G.B., 2002. Chapter 1 Mechanisms of phase-locking and frequency  
729 control in pairs of coupled neural oscillators. *Handb. Dyn. Syst.* 2, 3–54.  
730 doi:10.1016/S1874-575X(02)80022-4
- 731 Kuramoto, Y., 1991. Collective synchronization of pulse-coupled oscillators and excitable units.  
732 *Phys. D Nonlinear Phenom.* 50, 15–30. doi:10.1016/0167-2789(91)90075-K
- 733 Lachaux, J.P., Rodriguez, E., Martinerie, J., Varela, F.J., 1999. Measuring phase synchrony in  
734 brain signals. *Hum Brain Mapp* 8, 194–208.
- 735 Lowet, E., Roberts, M., Hadjipapas, A., Peter, A., van der Eerden, J., De Weerd, P., 2015. Input-  
736 Dependent Frequency Modulation of Cortical Gamma Oscillations Shapes Spatial  
737 Synchronization and Enables Phase Coding. *PLoS Comput. Biol.* 11, e1004072.  
738 doi:10.1371/journal.pcbi.1004072
- 739 Lowet, E., Roberts, M.J., Bonizzi, P., Karel, J., De Weerd, P., 2016. Quantifying Neural  
740 Oscillatory Synchronization: A Comparison between Spectral Coherence and Phase-  
741 Locking Value Approaches. *PLoS One* 11, e0146443. doi:10.1371/journal.pone.0146443
- 742 Maier, A., Adams, G.K., Aura, C., Leopold, D.A., 2010. Distinct superficial and deep laminar  
743 domains of activity in the visual cortex during rest and stimulation. *Front. Syst. Neurosci.* 4.  
744 doi:10.3389/fnsys.2010.00031
- 745 Maris, E., Fries, P., van Ede, F., 2016. Diverse Phase Relations among Neuronal Rhythms and  
746 Their Potential Function. *Trends Neurosci.* 39, 86–99. doi:10.1016/j.tins.2015.12.004
- 747 Miller, E.K., Buschman, T.J., 2013. Cortical circuits for the control of attention. *Curr. Opin.*  
748 *Neurobiol.* 23, 216–222. doi:10.1016/j.conb.2012.11.011
- 749 Palanca, B.J.A., DeAngelis, G.C., 2005. Does neuronal synchrony underlie visual feature  
750 grouping? *Neuron* 46, 333–46. doi:10.1016/j.neuron.2005.03.002
- 751 Pikovsky, A., Rosenblum, M., Kurths, J., Hilborn, R.C., 2002. Synchronization: A Universal  
752 Concept in Nonlinear Science. *Am. J. Phys.* 70, 655. doi:10.1119/1.1475332
- 753 Ray, S., Maunsell, J.H.R., 2010. Differences in gamma frequencies across visual cortex restrict  
754 their possible use in computation. *Neuron* 67, 885–96. doi:10.1016/j.neuron.2010.08.004
- 755 Ray, S., Ni, A.M., Maunsell, J.H.R., 2013. Strength of gamma rhythm depends on normalization.  
756 *PLoS Biol.* 11, e1001477. doi:10.1371/journal.pbio.1001477
- 757 Roberts, M.J., Lowet, E., Brunet, N.M., Ter Wal, M., Tiesinga, P., Fries, P., De Weerd, P., 2013.  
758 Robust gamma coherence between macaque V1 and V2 by dynamic frequency matching.  
759 *Neuron* 78, 523–36. doi:10.1016/j.neuron.2013.03.003
- 760 Sancristóbal, B., Vicente, R., Garcia-Ojalvo, J., 2014. Role of frequency mismatch in neuronal  
761 communication through coherence. *J. Comput. Neurosci.* 37, 193–208. doi:10.1007/s10827-  
762 014-0495-7
- 763 Schroeder, C.E., Tenke, C.E., Givre, S.J., Arezzo, J.C., Vaughan, H.G., 1991. Striate cortical  
764 contribution to the surface-recorded pattern-reversal vep in the alert monkey. *Vision Res.*  
765 31, 1143–1157. doi:10.1016/0042-6989(91)90040-C
- 766 Schwemmer, M.A., Lewis, T.J., 2012. Phase Response Curves in Neuroscience, in: *Phase*  
767 *Response Curves in Neuroscience.* pp. 3–31. doi:10.1007/978-1-4614-0739-3
- 768 Sclar, G., Maunsell, J.H.R., Lennie, P., 1990. Coding of image contrast in central visual  
769 pathways of the macaque monkey. *Vision Res.* 30, 1–10. doi:10.1016/0042-6989(90)90123-



770 3  
771 Sirota, A., Montgomery, S., Fujisawa, S., Isomura, Y., Zugaro, M., Buzsáki, G., 2008.  
772 Entrainment of neocortical neurons and gamma oscillations by the hippocampal theta  
773 rhythm. *Neuron* 60, 683–697. doi:10.1016/j.neuron.2008.09.014  
774 Steriade, M., McCormick, D.A., Sejnowski, T.J., 1993. Thalamocortical oscillations in the  
775 sleeping and aroused brain. *Science* 262, 679–685. doi:10.1126/science.8235588  
776 Stettler, D.D., Das, A., Bennett, J., Gilbert, C.D., 2002. Lateral Connectivity and Contextual  
777 Interactions in Macaque Primary Visual Cortex. *Neuron* 36, 739–750. doi:10.1016/S0896-  
778 6273(02)01029-2  
779 Tiesinga, P., Fellous, J.-M., Sejnowski, T.J., 2008. Regulation of spike timing in visual cortical  
780 circuits. *Nat. Rev. Neurosci.* 9, 97–107. doi:10.1038/nrn2315  
781 Tiesinga, P., Sejnowski, T.J., 2009. Cortical enlightenment: are attentional gamma oscillations  
782 driven by ING or PING? *Neuron* 63, 727–732. doi:10.1016/j.neuron.2009.09.009  
783 Tiesinga, P.H., Fellous, J.-M., Salinas, E., José, J. V, Sejnowski, T.J., 2005. Inhibitory synchrony  
784 as a mechanism for attentional gain modulation. *J. Physiol. Paris* 98, 296–314.  
785 doi:10.1016/j.jphysparis.2005.09.002  
786 Tiesinga, P.H., Sejnowski, T.J., 2010. Mechanisms for Phase Shifting in Cortical Networks and  
787 their Role in Communication through Coherence. *Front Hum Neurosci* 4, 196.  
788 doi:10.3389/fnhum.2010.00196  
789 Traub, R.D., Whittington, M. a, Colling, S.B., Buzsáki, G., Jefferys, J.G., 1996. Analysis of  
790 gamma rhythms in the rat hippocampus in vitro and in vivo. *J. Physiol.* 493 ( Pt 2, 471–84.  
791 Vaknin, G., DiScenna, P.G., Teyler, T.J., 1988. A method for calculating current source density  
792 (CSD) analysis without resorting to recording sites outside the sampling volume. *J.*  
793 *Neurosci. Methods* 24, 131–135. doi:10.1016/0165-0270(88)90056-8  
794 Vinck, M., Bosman, C.A., 2016. More Gamma More Predictions: Gamma-Synchronization as a  
795 Key Mechanism for Efficient Integration of Classical Receptive Field Inputs with Surround  
796 Predictions. *Front. Syst. Neurosci.* 10, 35. doi:10.3389/fnsys.2016.00035  
797 Vinck, M., Lima, B., Womelsdorf, T., Oostenveld, R., Singer, W., Neuenschwander, S., Fries, P.,  
798 2010. Gamma-phase shifting in awake monkey visual cortex. *J Neurosci* 30, 1250–1257.  
799 doi:10.1523/JNEUROSCI.1623-09.2010  
800 Wang, S., Musharoff, M.M., Canavier, C.C., Gasparini, S., 2013. Hippocampal CA1 pyramidal  
801 neurons exhibit type 1 phase-response curves and type 1 excitability. *J. Neurophysiol.* 109,  
802 2757–66. doi:10.1152/jn.00721.2012  
803 Winfree, A.T., 1967. Biological rhythms and the behavior of populations of coupled oscillators.  
804 *J. Theor. Biol.* 16, 15–42. doi:10.1016/0022-5193(67)90051-3  
805 Winfree, A.T., 2001. *The Geometry of Biological Time*.  
806 Womelsdorf, T., Schoffelen, J.-M., Oostenveld, R., Singer, W., Desimone, R., Engel, A.K.,  
807 Fries, P., 2007. Modulation of neuronal interactions through neuronal synchronization.  
808 *Science* 316, 1609–1612. doi:10.1126/science.1139597  
809 Zhou, H., Schafer, R.J., Desimone, R., 2016. Pulvinar-Cortex Interactions in Vision and  
810 Attention. *Neuron* 89, 209–220. doi:10.1016/j.neuron.2015.11.034  
811  
812  
813  
814  
815

816

817