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## **Theta Oscillations Organize Spiking Activity in Higher-Order Visual Thalamus during Sustained Attention**

**Chunxiu Yu<sup>1</sup>, Yuhui Li<sup>1</sup>, Iain M. Stitt<sup>1</sup>, Zhe Charles Zhou<sup>1</sup>, Kristin K. Sellers<sup>1</sup> and Flavio Frohlich<sup>1,2,3,4,5</sup>**

<sup>1</sup>*Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*

<sup>2</sup>*Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*

<sup>3</sup>*Department of Biomedical Engineering, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*

<sup>4</sup>*Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*

<sup>5</sup>*Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599, USA*

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**Correspondence should be addressed to:** Flavio Frohlich, 115 Mason Farm Rd. NRB 4109F, Chapel Hill, NC 27599, USA. Email: [flavio\\_frohlich@med.unc.edu](mailto:flavio_frohlich@med.unc.edu)

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2 **Sustained Attention**

3

4 Chunxiu Yu<sup>1</sup>, Yuhui Li<sup>1</sup>, Iain M. Stitt<sup>1</sup>, Zhe Charles Zhou<sup>1</sup>, Kristin K. Sellers<sup>1</sup>, Flavio  
5 Frohlich<sup>1,2,3,4,5</sup>

6

7 Correspondence should be addressed to: Flavio Fröhlich, 115 Mason Farm Rd. NRB 4109F,  
8 Chapel Hill, NC. 27599. Email: flavio\_frohlich@med.unc.edu

9

10 1 Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill NC 27599,  
11 USA

12 2 Department of Neurology, University of North Carolina at Chapel Hill, Chapel Hill NC 27599,  
13 USA

14 3 Department of Biomedical Engineering, University of North Carolina at Chapel Hill, Chapel  
15 Hill NC 27599, USA

16 4 Department of Cell Biology and Physiology, University of North Carolina at Chapel Hill,  
17 Chapel Hill NC 27599, USA

18 5 Neuroscience Center, University of North Carolina at Chapel Hill, Chapel Hill NC 27599,  
19 USA

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27 **Conflict of Interest**

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31

32 **Abstract**

33 Higher-order visual thalamus plays a fundamental but poorly understood role in attention-  
34 demanding tasks. To investigate how neuronal dynamics in higher-order visual thalamus are  
35 modulated by sustained attention, we performed multichannel electrophysiological recordings in  
36 the lateral posterior-pulvinar complex (LP/pulvinar) in the ferret (*Mustela putorius furo*). We  
37 recorded single unit activity and local field potential during the performance of the 5-choice  
38 serial reaction time task (5-CSRTT) that is used in both humans and animals as an assay of  
39 sustained attention. We found that half of the units exhibited an increasing firing rate during the  
40 delay period before stimulus onset (attention-modulated units). In contrast, the non-attention-  
41 modulated units responded to the stimulus, but not during the delay period. Spike-field  
42 coherence of only the attention-modulated neurons significantly increased from the start of the  
43 delay period until screen touch, predominantly in the theta frequency band. In addition, theta  
44 power and theta-gamma phase-amplitude coupling were elevated throughout the delay period.  
45 Our findings suggest that the theta oscillation plays a ~~central~~ role in orchestrating thalamic  
46 signaling during sustained attention.

47

48 **Significance**

49 Impaired sustained attention can be deadly, as illustrated by the number of motor vehicle  
50 accidents that are caused by drivers not reacting quickly enough to unexpected events on the  
51 road. Understanding how electrical signaling in higher-order visual nuclei, such as the  
52 LP/pulvinar, is modulated during tasks that require sustained attention is an important step in  
53 achieving a mechanistic understanding of sustained attention, which will eventually lead to new  
54 strategies to prevent and treat impairment in sustained attention.

55

56 **Introduction**

57 Sustained attention is defined as the allocation of processing resources to rare but important  
58 events during prolonged periods of time (Sarter, Givens et al. 2001). Sustained attention is a key  
59 element of attention models (Mirsky, Anthony et al. 1991) and integrates multiple behavioral  
60 processes including executive control for controlling competing impulses and executing planned  
61 actions to appropriate stimuli (Cohen, Sparling-Cohen et al. 1993).

62

63 In humans, sustained attention is typically measured with the continuous performance task  
64 (CPT), which requires the participant to respond to an infrequent stimulus over prolonged time.  
65 Neuroimaging studies support an active role of the fronto-parietal attention network in sustained  
66 attention (Lewin, Friedman et al. 1996) but subcortical structures have also been proposed to be  
67 part of the network substrate of sustained attention (Riccio, Reynolds et al. 2002). Sustained  
68 attention is not only impaired in attention deficit hyperactivity disorder (ADHD) (Barkley 1997,  
69 Bellgrove, Hawi et al. 2006, Johnson, Robertson et al. 2007) but also depression (Ronald Cohen,  
70 Ilan Lohr et al. 2001), bipolar disorder (Martínez-Arán, Vieta et al. 2000), and schizophrenia  
71 (Shi K. Liu, Chia-Hui Chiu et al. 2002). Interestingly, impairment of sustained attention persists  
72 in patients with bipolar disorder (CLARK, IVERSEN et al. 2002) and major depressive disorder  
73 (Paelecke-Habermann, Pohl et al. 2005) even after achieving remission.

74

75 In animal model species, one task that has been extensively used to delineate the substrate of  
76 sustained attention is the five-choice serial reaction time task (5-CSRTT) that probes spatial  
77 sustained attention (Bari, Dalley et al. 2008). In the 5-CSRTT, animals respond to a visual  
78 stimulus at one of five stimulus locations after a delay period. The 5-CSRTT is a widely used  
79 task that has provided fundamental insights into the cellular and molecular mechanisms of  
80 sustained attention, and is used for the evaluation of candidate compounds for the treatment of  
81 ADHD (Day, Pan et al. 2007).

82

83 Despite the extensive study of sustained attention at the behavioral level in both humans and  
84 animal models, surprisingly little is known about the circuit dynamics of sustained attention.  
85 Recently, we reported that the 5-CSRTT engaged synchrony of oscillatory activity in the fronto-

86 parietal network of the ferret (Sellers, Yu et al. 2016, Zhou, Salzwedel et al. 2016). Phase  
87 synchronization both at the microscale of neuronal action potentials and the mesoscale of the  
88 population synaptic activity reflected in the local field potential was elevated in the theta-  
89 frequency range.

90

91 In contrast, the role of subcortical structures in oscillatory network interactions during sustained  
92 attention has remained mostly unknown. The thalamus plays a major role in regulating the  
93 thalamo-cortical network dynamics that reflect vigilance levels (Llinas and Steriade 2006, Stitt,  
94 Zhou et al. 2017). Since vigilance requires sustained attention, we asked if higher-order thalamus  
95 is engaged in the 5-CSRTT. In particular, we investigated how spiking and oscillatory network  
96 activity is modulated during the delay period during which the animals pay attention to the  
97 potential stimulus locations.

98

99 **Materials and Methods**

100 Three spayed female ferrets (*Mustela putorius furo*, 4 months of age at the beginning of the  
101 experiments) were trained to reach satisfactory task performance and subsequently implanted  
102 with electrode arrays in the LP/Pulvinar complex for combining neurophysiological  
103 measurements with behavioral data collection. All procedures were approved by the Institutional  
104 Animal Care and Use Committee of the University of North Carolina at Chapel Hill and  
105 followed National Institutes of Health guidelines for the care and use of laboratory animals.

106

107 *Behavioral apparatus*

108 Ferrets were trained in a touch-screen based version of the 5-Choice Serial Reaction Time Task  
109 (5-CSRTT) (Bari, Dalley et al. 2008). Training took place in an enclosed and sound-attenuated  
110 custom-built operant chamber (51 x 61 x 61 cm<sup>3</sup>). The chamber consisted of a touch screen  
111 monitor (Acer T232HL 23-inch touch screen LCD display) covered with a black Plexiglass  
112 mask. The mask exhibited five equally sized square cut-outs (windows, 7 x 7 cm), in one of  
113 which the stimulus was presented in each trial. Below the openings, there was a shelf on which  
114 the animals could comfortably rest their front legs when nose-poking the touchscreen. The  
115 opposite wall was equipped with a lick spout centrally positioned 6 cm above the floor for water  
116 delivery combined with an infrared (IR)-based proximity detector and an LED light. The  
117 behavioral chamber also included a “house light” mounted on the ceiling of the chamber  
118 opposite the monitor to provide feedback for correct and incorrect trials and a speaker (HP  
119 Compact 2.0 speaker) to deliver auditory tones. Infrared videography was performed during all  
120 sessions (Microsoft LifeCam Cinema 720p HD Webcam with filter that blocks infrared light  
121 removed). The entire behavioral setup was controlled by a data acquisition device (USB 6212,  
122 National Instruments, Austin, TX) and custom-written Matlab scripts (Mathworks, Natick, MA)  
123 that used functionality from the Psychophysics toolbox (Brainard 1997) for precise temporal  
124 control of stimulus presentation.

125

126 *5-choice serial reaction time task (5-CSRTT)*

127 In the 5-CSRTT (Bari, Dalley et al. 2008), the animals initiated a trial by approaching the lick-  
128 spout at the rear end of the behavior chamber. Upon initiation, a 5 sec delay period started during  
129 which no stimuli were presented and the ferrets had to prepare and sustain attention to the five  
130 windows (cut-outs in the mask on the touchscreen). After the delay ended, a white solid square  
131 (stimulus) was randomly presented for 2 sec in one of five windows. For correct trials, touching  
132 the stimulus window during the 2 sec of stimulus presentation or in the first 2 sec after the  
133 stimulus was turned off (hold period, HP) triggered a 0.5 sec tone, illumination of the lick spout  
134 light, a water reward release (0.2 ml) at the lick spout (Fig. 1A, left). The lick spout light was on  
135 until the animal nose poked into the lick spout. For incorrect trials, touching a window before the  
136 stimulus onset (PreTouch) or touching an adjacent incorrect window after 5 sec delay  
137 (MissTouch), or failing to respond to the stimulus at all (NoTouch, omission) caused a 1 sec  
138 white noise auditory stimulus, illumination of the house light, and a subsequent 6 sec time-out  
139 period, in which no water was delivered (Fig. 1A, right). Following the 8 sec inter-trial interval  
140 after correct responses or 6 sec time-out period after incorrect responses, the lick-spout light  
141 turned on to indicate the availability of the next trial. The session was terminated after 60 trials  
142 or 40 min, whichever came first. Criteria of >80% accurate stimulus detection and <20%  
143 omission for at least five consecutive sessions were used during the training.

144

#### 145 *Behavioral training*

146 Ferrets were water deprived and received free access to water (60ml) each day after training and  
147 testing. Body weight was monitored daily and never dropped below 85% which would have  
148 triggered discontinuation of water deprivation by protocol. The ferrets underwent a multistep  
149 training plan that included five subsequent training levels: 1, arena habituation 2, touch-reward  
150 association 3, single stimulus-reward association 4, task initiation 5, 5-CSRTT. Following this  
151 training schedule, the ferrets were successively advanced to the final task, in which the ferrets  
152 were required to initiate the trial by nose-poking the water spout. Ferrets were trained and tested  
153 daily on a 5 days on / 2 days off schedule.

154

#### 155 *Surgery*

156 After successful training, the ferrets were surgically implanted with a chronic multichannel  
157 electrode array (2x8 tungsten electrode array, 250 $\mu$ m spacing, low-impedance reference  
158 electrode with the same length on the same array, MicroProbes Inc, Gaithersburg, MD) in  
159 LP/Pulvinar. Surgical procedure was similar to those previously described (Sellers, Yu et al.  
160 2016, Zhou, Yu et al. 2016). Briefly, ferrets were first injected with ketamine/xylazine (30 mg/kg  
161 of ketamine, 1-2 mg/kg of xylazine, IM) for anesthesia induction, and then were intubated and  
162 anesthetized with inhaled isoflurane (1.5-2%) in 100% medical oxygen (mechanically ventilated,  
163 10-11 cc volume, 50 bpm). Body temperature was maintained between 38-39°C with a water  
164 heating blanket. Electrocardiogram, end-tidal CO<sub>2</sub> and partial oxygen saturation were monitored  
165 throughout surgery. The skull was exposed and a craniotomy was performed over the target area  
166 (centered at 13 mm anterior to lambda, 3.6 mm lateral from midline) (Yu, Sellers et al. 2015). A  
167 small slit was made into the dura before insertion of electrode array (7.4 mm from cortical  
168 surface). Electrode arrays were secured in place with dental cement and several non-penetrating  
169 skull screws. A separate ground wire was implanted in cortex of the same hemisphere. The  
170 wound margins were sutured together and anesthesia was reversed. Ferrets received standard  
171 postoperative care with 3 days of meloxicam for pain relief (0.2 mg/kg, IM) and 7 days of  
172 clavamox to prevent infection (12.5-13mg/kg, oral).

173

#### 174 *Electrophysiological recording*

175 The animals were given two weeks of recovery time before they were retrained on the final task  
176 to again reach stable performance (typically a few sessions). At this point, wireless  
177 electrophysiological recordings were performed with a MCS 2100 system (Multichannel  
178 Systems, Reutlingen, Germany). Broadband data (1 Hz to 5 kHz) were collected (sampling rate:  
179 20 kHz) and digitally stored for offline analysis. Simultaneously with acquisition of the neuronal  
180 data, time-locked acquisition of relevant behavioral events (trial initiation, screen touch, reward  
181 retrieval) was performed through digital input channels on the wireless recording system.  
182 Behavioral data were stored separately by a custom-written Matlab script. In addition, high-  
183 resolution infrared videography (30 frames/s) was performed that was synchronized to the  
184 neuronal data acquisition.

185

186 *Histology*

187 To verify electrode locations in the LP/pulvinar complex, electrolytic lesions were induced at the  
188 completion of recording by passing current through the four electrodes (two middle and two  
189 corner) of the microelectrode array (5  $\mu$ A, 10s, unipolar). The damage visible in the sections  
190 stem from this lesioning protocol. Animals were then humanely euthanized with an overdose of  
191 sodium pentobarbital (IV injection) and perfused with 0.1M PBS and 4% paraformaldehyde  
192 solution in 0.1M PBS. The brains were post-fixed and cut in 60  $\mu$ m coronal sections using a  
193 cryostat (CM3050S, Leica Microsystems), and then stained for cytochrome oxidase (Yu, Sellers  
194 et al. 2016). Imaging was acquired using a widefield microscope (Nikon Eclipse 80i, Nikon  
195 Instruments, Melville, NY). Electrodes outside of LP/pulvinar were excluded from analysis.

196

197 *Data analysis*

198 Behavioral data were analyzed with custom-written Matlab scripts. The main  
199 measurements of interest were: (1) identity of the window touched, (2) reaction time after visual  
200 stimulus onset, and (3) animal location relative to windows on touchscreen. Equally, MissTouch,  
201 NoTouch and PreTouch trials were also tracked. Performance accuracy in detecting the stimulus  
202 was defined as percentage of the number of correct responses divided by the total number of  
203 correct and incorrect (MissTouch) responses. The video recordings were analyzed offline with  
204 Ethovision XT (Noldus, Leesburg, VA) and the three-point animal-tracking module to detect the  
205 animal location (sample rate 30 frames/s). Heatmaps were generated for demonstration of animal  
206 trajectories. We also manually reviewed video recordings and coded the orientation of the animal  
207 immediately prior to the stimulus onset. Only correct trials with the animal orienting to the  
208 screen at the time of stimulus onset were included in further analysis.

209

210 Electrophysiology data were analyzed by a combination of custom-written Matlab scripts. Trials  
211 exhibiting simultaneous large amplitude deflections across channels (artifacts in  
212 electrophysiological recordings) were excluded. Single units were extract with the Plexon  
213 Offline Sorter (Plexon Inc, Dallas, TX) spike sorting software. Briefly, multiunit activity was  
214 detected by high-pass filtering the raw continuous data with a Butterworth 2nd order filter with  
215 300Hz cut-off. Action potentials were detected by threshold crossing (-4 times the standard  
216 deviation of the high-pass filtered signal). Spikes were identified, collected and sorted using the

217 T-distribution expectation maximization algorithm (Shoham, Fellows et al. 2003) and manual  
218 inspection with the Plexon Offline Sorter. Spikes with shorter than 1 msec refractory period were  
219 removed. Neural activity within a window of -7 to 5 sec aligned on stimulus onset was averaged  
220 in 200-msec bins and averaged across trials to construct the peri-stimulus time histogram  
221 (PSTH). The PSTHs were then z-scored by subtracting the mean baseline firing rate (measured  
222 from a baseline window from -2 to 0 second before trial initiation) and dividing by the standard  
223 deviation. To classify “attention-modulated” vs. “non-attention-modulated” units, neural activity  
224 within 2 second before the stimulus onset was compared to a baseline window from -2 to 0  
225 second before the trial initiation (two-tailed t test,  $p < 0.05$ ). The 2 sec window was chosen based  
226 on visual inspection of the behavioral video. The ferrets usually began facing the windows and  
227 remained in an oriented posture around 2 second before stimulus onset.

228

229 To investigate the rhythmic structure of LP/pulvinar activity, local field potentials (LFP) were  
230 computed by low-pass filtering the raw continuous data with a Butterworth 2nd order filter with  
231 300Hz cut-off. To study the synchrony between LP/Pulv spikes and the LFP at different epochs  
232 during the task, we computed the spike-field coherence of simultaneously recorded spike trains  
233 and LFP using multi-taper analysis provided by the Chronux data analysis toolbox (Saalmann,  
234 Pinsk et al. 2012). The spike-field coherence was calculated in 2 sec windows using the  
235 ‘*coherencycpt*’ function for each epoch (before initiation, before stimulus onset, before screen  
236 touch and after screen touch). We corrected coherence values to remove the effects of unequal  
237 number of trials in each session (Bokil, Purpura et al. 2007, Saalmann, Pinsk et al. 2012). The  
238 corrected spike-field coherence was computed using the formula of  $T(f) = \text{atanh}(C(f)) - 1/(df-2)$ ,  
239 where  $C(f)$  is the raw coherence value;  $df$  is the degrees of freedom;  $df = 2 * K * N$ , where  $K$  is the  
240 number of tapers and  $N$  is the number of trials. The corrected coherence estimates were pooled  
241 across the population. Two-way ANOVA was used to compare the modulation of the coherence  
242 at different epochs during the task. We calculated the spike-triggered average (STA) of the LFP  
243 by extracting segments of the LFP from -1.2 to 1.2 sec relative to the spike times of individual  
244 single units. Subsequently, all these LFP segments were aligned and averaged to compute the  
245 STA of the LFP. As a control, we shuffled the spike trains across different trials and re-computed  
246 the STA of the LFP. This manipulation only disrupts the relationship between the spikes and the  
247 LFP but preserves the temporal structure of the spike train within individual trials.

248

249 Cross-frequency phase-amplitude coupling (PAC) was computed to assess the degree with which  
 250 high frequency oscillations are temporally organized by the phase of low frequency oscillations  
 251 in the LP/Pulvinar. PAC was defined as the phase locking value (PLV) between low frequency  
 252 signals and amplitude fluctuations of high frequency signals occurring at the lower carrier  
 253 frequency. First, an LFP signal  $x(t)$  was convolved with a low frequency Morlet wavelet with  
 254 carrier frequency  $f_1$

$$X(t, f_1) = x(t) * w(t, f_1)$$

255 where  $*$  denotes the convolution operation. Then the analytic amplitude of the same signal  $x(t)$   
 256 at a higher carrier frequency  $f_2$  was convolved with a wavelet with carrier frequency  $f_1$

$$X(t, f_2) = |x(t) * w(t, f_2)| * w(t, f_1)$$

257 The instantaneous phase of each time series was then computed by taking the argument of the  
 258 real and imaginary components of the time frequency estimates. Finally, PAC is defined as the  
 259 PLV between low and high frequency signal components

$$PAC(f_1, f_2) = \frac{1}{N} \left| \sum_{n=1}^N e^{i(\theta_n^{f_1} - \theta_n^{f_2})} \right|$$

260 PAC values were bound between 0 and 1, with 0 indicating no relationship, and 1 perfect  
 261 alignment of high frequency amplitude modulations with low frequency phase. To examine PAC  
 262 extensively in frequency-frequency parameter space, we computed PAC between low  
 263 frequencies ( $f_1$ ) ranging from 1 to 10 Hz in 0.25 Hz steps, and high frequencies ( $f_2$ ) from 10 to  
 264 80 Hz in 1 Hz steps. This analysis revealed prominent PAC between theta and gamma  
 265 frequencies in LP/Pulvinar. After identifying this frequency-frequency band of interest, we  
 266 repeated analysis using a phase preserving 4<sup>th</sup> order Butterworth filter and Hilbert transform  
 267 instead of Morlet wavelet convolution to maximally capture time frequency fluctuations in the  
 268 theta/gamma band of interest (theta 3-6 Hz, gamma 30-60 Hz). Finally, to investigate how  
 269 theta/gamma PAC is modulated by the 5-CSRTT, we computed PAC in sliding windows of 200  
 270 msec (step size 100 msec) aligned to stimulus onset.

271

272

273 **Results**274 *Behavioral Performance*

275 To probe the role of LP/Pulvinar neuronal dynamics in sustained attention, we trained 3 ferrets to  
276 perform a five choice serial reaction time task (5-CSRTT, Fig. 1A-B). The 5-CSRTT was  
277 designed as a task in which freely moving animals make a choice in each trial to get a reward.  
278 Trials were self-initiated at a lick spout in the back of the behavioral apparatus and a touch-  
279 screen with five stimulus locations was used to display the targets and capture the behavioral  
280 responses. All ferrets reached criterion performance across recording sessions with high accuracy  
281 (Fig. 1C, Mean  $\pm$  SEM, Ferret 1: 88.1%  $\pm$  1.85%, Ferret 2: 98.7%  $\pm$  0.38%, Ferret 3: 99.4%  $\pm$   
282 0.29%) and low omission rates (Ferret 1: 12.6  $\pm$  2.77%, Ferret 2: 7.10%  $\pm$  1.40%, Ferret 3:  
283 16.7%  $\pm$  2.12%). Video tracking data confirmed that animals moved towards the screen during  
284 the delay period (Fig. 1D), with animals reaching their final position close to the screen  
285 approximately 2 seconds before stimulus onset. This implies that ferrets allocated attention to the  
286 stimulus windows in anticipation of the visual stimulus during this time period. In addition, the  
287 reaction time distribution for correct trials indicated that animals responded quickly to stimuli,  
288 with most responses within 2 seconds of stimulus onset (Fig. 1E). We used criteria of > 80%  
289 accurate stimulus detection and < 20% omission for at least five consecutive sessions to  
290 determine that an animal has learnt the task. Typically, 12 sessions were used before the surgery.  
291 After surgery, about 1-3 sessions of recovery training were needed before the behavioral  
292 performance reached the criteria again and the electrophysiological recording were started. We  
293 then asked if neuronal firing in the LP/Pulvinar was modulated during the delay period.

294

295 *Single Unit Activity in LP/Pulvinar*

296 We implanted microelectrode arrays into LP-Pulvinar and confirmed implantation locations  
297 through histological reconstruction of the recording sites (Fig. 2A). We found that about half of  
298 the LP/Pulvinar single neurons (n = 130/259 units) displayed a progressively increasing firing  
299 rate during the delay period of the task (Fig. 2B-E). Since no stimuli were present in any of the  
300 windows during the delay period, such elevated firing rates suggest that the excitability of this  
301 subpopulation of LP/Pulvinar neurons is modulated by behavioral or mental engagement of the  
302 animal with the possible locations of the future stimulus (referred to as attention-modulated). The  
303 remaining 50% of neurons (n = 129/259) did not exhibit significant changes in firing rate during

304 the delay period. However, both attention-modulated and non-attention-modulated LP/Pulvinar  
305 neurons displayed increases in firing rate in response to the visual stimulus. This increase was  
306 significantly stronger for attention-modulated neurons (Unpaired t test,  $t(257) = 10.73$   $p < 0.001$ ).  
307 Furthermore, the attention-modulated neurons had higher firing rate in the correct trials  
308 compared to in the incorrect trials (Figure 2D, solid red line compared to dotted red line, paired t  
309 test,  $t(129) = 3.23$ ,  $p = 0.0016$ ). Thus the delay period of the 5-CSRTT led to a ramping up of  
310 spiking activity in a subpopulation of LP/Pulvinar neurons which were correlated to the  
311 behavioral performance.

312

### 313 *Modulation of Spike-Field Coherence in the Theta Band*

314 We next asked if the task-related activity of the neurons in LP/Pulvinar exhibited a mesoscale  
315 organization that would be reflected in the LFP. To answer this question, we computed spike-  
316 field coherence (SFC) of both attention-modulated and non-modulated neuron subpopulations  
317 during different epochs of trials. We found SFC in the theta band (~5 Hz) throughout task  
318 performance (Fig. 3). We further confirmed the importance of the relationship between thalamic  
319 spikes and the theta oscillation by showing that the spike-triggered average (STA) of the LFP  
320 exhibits rhythmic structure in the theta band (inset in Fig. 3B). Strikingly, SFC in the theta band  
321 differed for attention-modulated and non-modulated neurons. A two-way ANOVA with neuronal  
322 response type (“attention-modulated” or “non-modulated”) and task segments (before initiation,  
323 before stimulus onset, before touch and after touch) as factors revealed a significant main effect  
324 of response type ( $F(1,1035) = 55.8$ ,  $p < 0.001$ ), main effect of timing ( $F(3,1035) = 4.04$ ,  $p =$   
325  $0.007$ ), and significant interaction between these factors ( $F(3,1035) = 4.07$ ,  $p = 0.007$ ). Post-hoc  
326 comparison showed that SFC in the theta frequency band was significantly higher for attention-  
327 modulated neurons than for non-modulated neurons during all trial epochs (multiple-comparison  
328 with Turkey-Kramer method, before initiation,  $p < 0.001$ , before stimulus onset,  $p = 0.001$ ,  
329 before touch,  $p < 0.001$ ), with the exception of the period after the screen-touch ( $p = 0.91$ ).  
330 While no changes in theta SFC was observed across task epochs for non-modulated neurons,  
331 theta SFC was significantly higher before touch than before trial initiation for attention-  
332 modulated neurons ( $p = 0.03$ ). These results suggest that neurons whose activity fluctuated with  
333 attention selectively synchronized to theta rhythms based on behavioral demands throughout the  
334 task.

335

336 *Theta-Gamma Phase Amplitude Coupling during Attention Allocation*

337 Since theta rhythms selectively synchronized the spiking activity of attention-modulated  
338 neurons, we next examined if the amplitude of theta rhythms was modulated in a similar way by  
339 sustained attention during the 5-CSRTT. Indeed, following trial initiation we observed an  
340 increase in theta power that remained elevated during the sustained attention period (Fig. 4A).  
341 Theta power then peaked approximately 400ms after the presentation of the visual stimulus,  
342 before falling to levels lower than before trial initiation. Theta rhythms have been observed  
343 across several cortical and subcortical brain regions, and have been implicated in the functions as  
344 diverse as working memory and spatial navigation (Frohlich 2016). However, these functions of  
345 theta oscillations are underpinned by one unifying mechanism: lower frequency theta oscillations  
346 temporally coordinate higher frequency gamma oscillations through phase amplitude coupling  
347 (PAC). Therefore, to test if theta oscillations in LP/Pulvinar behaved in a similar way to theta  
348 rhythms observed in other brain regions, we computed PAC between the phase of low frequency  
349 (< 10Hz) and the amplitude of high frequency LP/Pulvinar LFP signals (15-80 Hz). This analysis  
350 revealed that the amplitude of gamma oscillations (30-60 Hz) was temporally coupled to the  
351 phase of theta oscillations (4-6 Hz, Fig. 4B, PAC =  $0.29 \pm 0.01$  SEM), confirming that  
352 LP/Pulvinar theta oscillations exhibit similar cross-frequency interaction as theta observed in  
353 other brain regions.

354 If theta/gamma PAC represented an underlying mechanism that LP/Pulvinar uses to selectively  
355 synchronize cortical inputs and outputs based on behavioral demands, then one would expect the  
356 strength of theta/gamma PAC to fluctuate across trials of the 5-CSRTT. To test this hypothesis,  
357 we computed theta/gamma PAC in a temporally resolved manner across the trial. We indeed  
358 found task-dependent modulation of theta/gamma PAC during performance, where PAC was  
359 significantly elevated throughout the sustained attention period, and maintained a high level until  
360 screen touch (Fig 4C, paired t-test for PAC values between delay and baseline,  $t(30) = 4.51$ ,  $p <$   
361  $0.001$ ,  $n = 31$  recording sessions). We further examined gamma power across the trials. In  
362 contrast to the time-course of theta power and theta/gamma PAC, we found a significant  
363 reduction in gamma power during the sustained attention period (Fig 4D, paired t-test,  $t(30) =$   
364  $2.60$ ,  $p = 0.01$ ). Collectively, these results indicate that even though gamma power is reduced

365 during sustained attention, ongoing fluctuations in gamma amplitude are more tightly locked to  
366 the phase of LP/Pulvinar theta oscillations in a behaviorally dependent manner.

367

368 **Discussion**

369 We have shown that the LP/Pulvinar complex exhibits neuronal dynamics that are modulated  
370 during the 5-CSRTT, in particular during the delay period before onset of the stimulus. We  
371 found that oscillatory activity in the theta frequency binds the neurons that were activated during  
372 the delay period. Neuronal firing of these attention-modulated neurons exhibited a ramp-like  
373 increase in their firing rate during the delay period. These results suggest that the LP/Pulvinar  
374 may play a functional role in sustained attention.

375

376 The pulvinar has only recently become a brain area of wider interest and surprisingly little is  
377 known about its function. As a major part of the visual thalamus, the pulvinar appears to play an  
378 important role in the control of visual processing and attention (Saalmann and Kastner). Two  
379 recent studies reported somewhat different findings with regards to the role of pulvinar in  
380 modulating cortical network dynamics in tasks that required selective spatial attention, which is  
381 conceptually distinct from the sustained attention investigated in our study. The work by  
382 Saalmann and colleagues (Saalmann, Pinsk et al. 2012) identified enhanced effective  
383 connectivity from pulvinar to cortical areas in the alpha frequency band for attended stimuli. In  
384 contrast, work by Zhou and colleagues (Zhou, Schafer et al.) focused on gamma-band effective  
385 connectivity that was directed from cortex to pulvinar, however, they also found an increase in  
386 alpha effective connectivity from pulvinar to cortex. Interestingly, inactivation of the pulvinar  
387 caused not only a loss of the attentional gain in the cortical stimulus representation but an overall  
388 drop in activity below baseline for the unattended stimuli. Thus, these results support a  
389 fundamental role of the pulvinar in maintaining and perhaps guiding cortical activity in attention-  
390 demanding tasks. Together with our results, these studies suggest that while the pulvinar is  
391 involved in multiple domains of attention, the corresponding activity signatures may be distinct.

392

393 Other subunits of thalamus also appear to play a role in attention. In the context of selective  
394 attention to either visual or auditory stimuli, the medio-dorsal thalamus that forms a recurrent  
395 loop with prefrontal cortex plays a key role in amplifying PFC activity that is specific to the  
396 stimulus modality used on a given trial (Schmitt, Wimmer et al. 2017). In addition, the nucleus  
397 reticularis thalami, which contains inhibitory neurons that provide inhibition to other thalamic  
398 areas, is recruited in the same task (Wimmer, Schmitt et al. 2015). Although these studies have

399 investigated other types of attention than the sustained attention probed with the 5-CSRTT they,  
400 in agreement with our results, propose a role of the thalamus in allocation of processing  
401 resources.

402

403 Generators of theta oscillations have been previously described in the thalamus of animal models  
404 (Tsanov, Chah et al. 2011) and humans (Sweeney-Reed, Zaehle et al. 2014). Theta rhythms in  
405 the LP/pulvinar of the cat were modulated by the state of vigilance and differed from theta  
406 oscillations recorded from hippocampus (Crighel, Kreindler et al. 1978). In humans, thalamic  
407 theta rhythms, in particular the anterior thalamic nucleus, have been implicated in memory  
408 formation (Sweeney-Reed, Zaehle et al. 2015). In addition, human theta oscillations exhibit  
409 phase-amplitude coupling with higher-frequency oscillations in the range of 80 to 150 Hz  
410 (Sweeney-Reed, Zaehle et al. 2017). Despite the differences in the frequency of the amplitude-  
411 modulated signal and the thalamic area, the parallel to our findings of theta oscillations  
412 modulating gamma oscillation is of note. In quite a different context, theta bursting in thalamus  
413 is considered to be a signature of what is called thalamocortical dysrhythmia syndrome (Llinas  
414 and Steriade 2006). In this model, aberrant theta oscillations (in the form of bursts) emerge due  
415 to the deinactivation of the transient, low-threshold calcium current due to deafferentation or  
416 other pathology. Together with the fact that thalamic theta oscillations are associated with  
417 decreased vigilance, the question arises why we found an increase in the theta oscillations in the  
418 delay period of the 5-CSRTT. One potential answer derives from the comparison of first-order  
419 and higher-order thalamic structures. High-order thalamic structures such as the LP/Pulvinar  
420 exhibit a substantially larger fraction of rhythmically bursting cells in the awake state  
421 (Ramcharan, Gnadt et al. 2005). Thus, rhythmic synchronized activity in higher-order thalamus  
422 could serve as a “wake-up call” to cortex due to the enhanced postsynaptic effect of such  
423 synchronized thalamic activity and thus support sustained attention

424

425 The functional characterization of thalamic networks in ferrets is in its infancy. Little is known  
426 about the connectivity of different thalamic nuclei. We recently reported neurochemical  
427 subdivision of what we referred to as the LP/Pulvinar complex (Yu, Sellers et al. 2016). By  
428 combining tracer techniques and multisite electrophysiology in the anesthetized animal we  
429 showed an agreement of structural and functional connectivity between the lateral aspect of the

430 LP/Pulvinar complex and visual cortex. However, we can assume that this thalamic area also  
431 connects to other, higher-order (visual) areas such as posterior parietal cortex. Thus, we propose  
432 that thalamic activity may coordinate cortical activity in the visual areas for successful execution  
433 of the 5-CSRTT. Future studies are need to further examine and test this proposed conceptual  
434 model. It is worth noting that the nature of extracellular electrophysiology does not allow for the  
435 identification of specific cell types within an area. However, we are confident about the  
436 anatomical location of the neurons described in this study based on our histological  
437 reconstructions of the electrode tracks and our previous work on the anatomy of the LP/Pulvinar  
438 complex. An additional source of confusion is the different nomenclature for seemingly similar  
439 structures across species, with different naming conventions for carnivores that include the ferret  
440 (Jones 2007). We decided to use the broader term of the LP/Pulvinar complex for extrageniculate  
441 visual thalamus to avoid dogmatic disputes of researchers across model species (Kaas 2007). We  
442 argue that the structural connectivity (as previously reported by us) is the more relevant  
443 information that the specific naming scheme chosen.

444

445 To our knowledge, this is the first electrophysiological study of higher-order thalamus in  
446 sustained attention using the 5-CSRTT. However, as any scientific study, the work presented  
447 here has limitations. First, our findings on the organization of the network activity in the  
448 LP/Pulvinar complex are correlative in nature and we have not used causal circuit interrogation  
449 strategies such as optogenetics. The use of these techniques in larger-brain species such as ferrets  
450 and non-human primates is still under active development and has remained in its infancy in  
451 comparison to the investigations of the mouse brain. We argue that the synthesis of research  
452 from different model species with different levels of brain complexity substantially advances the  
453 field even if the toolsets vary between them. Nevertheless, the development of targeted causal  
454 circuit perturbations in species such as the ferret are of fundamental importance and we recently  
455 reported the first successful use of optogenetics in the awake behaving ferret (Zhou, Yu et al.  
456 2016). Second, we have not parameterized our tasks for a more detailed dissection of the  
457 behavioral components. For example, different lengths of the delay period and presentation of  
458 distracting stimuli during the delay period are experimental manipulations that will allow the  
459 future testing of hypotheses built on the results from the study presented here. Importantly,  
460 introducing competing sensory stimuli would transform the task to one that probes selective

461 attention (Robbins 2002), which differs from sustained attention. Third, and lastly, we did not  
462 investigate how the thalamic signaling modulated cortico-cortical and cortico-thalamo-cortical  
463 interactions. The goal of the current study was to delineate the role of the LP/Pulvinar complex  
464 in the ferret during sustained attention. Similar investigations with multiple electrode arrays not  
465 only in thalamus but also cortical areas that are anatomically connected will be the next step.

466

467 In conclusion, our study suggests that the higher-order visual thalamus is engaged during  
468 sustained attention and that oscillatory activity in the theta frequency bands organizes the neural  
469 firing of the subpopulation modulated by sustained attention. Our findings reinforce the  
470 importance of the thalamus in cognitive constructs such as attention that are often studied from a  
471 cortico-centric perspective.

472

473 **Figure Legends**

474

475 *Figure 1. Sustained Attention Task in Freely-Moving Ferrets*

476 **A** Illustration of trial sequences of the 5-CSRTT. Each trial begins with illumination of the water  
477 spout, which is centrally placed on the back wall of the chamber. The ferret initiates the trial by  
478 approaching the water spout, which is equipped with an infrared proximity sensor. Then, the  
479 spout light is extinguished and the 5 sec delay period starts during which the animal is required  
480 to sustain attention to the five windows on the front wall of the chamber. A white solid square  
481 (stimulus) will randomly present in one of five windows after the delay ends. Nose-poke to the  
482 stimulus window during stimulus presentation (2 sec) or in the first 2 sec after stimulus offset  
483 (hold period, HP) triggers a tone and delivery of water reward at the spout (correct trial, left).  
484 Touch by the ferret is indicated with an asterisk. If the ferret responds before the stimulus  
485 (PreTouch), or touches an incorrect window (MissTouch), or fails to respond before the end of  
486 the HP (Omission), a 6 sec time-out (TO) period is introduced where the house light is on and no  
487 water is delivered (right). After collecting the reward (8 sec time window) or at the end of the  
488 TO period, a new trial can be started.

489 **B** Representative photographs of one animal during a single trial: a, initiation; b, turn to the  
490 stimulus windows (numbered 1 through 5); c-d, paws on the platform and checking for  
491 occurrence of stimulus; e, stimulus on; f, find the stimulus; g, nose poke the stimulus window; h,  
492 turn back to collect the reward; I, collect the reward; j, complete trajectory for a single trial  
493 obtained from video tracking. K, heatmap of animal locations during the session. Time stamps  
494 are shown in the corner of each frame.

495 **C** Behavioral performance. Mean accuracy and omission rates across sessions. Error bars:  
496 Standard error of the mean (SEM) across sessions.

497 **D** Mean distance between animal location and stimulus location as a function of time for correct  
498 trials. The shorter distances to middle windows (W2 – W4) indicate that animals were centered  
499 relative to the stimulus windows before stimulus onset.

500 **E** Distribution of touch reaction times for correct trials. In most trials, the correct window was  
501 touched during stimulus presentation (RT < 2 sec).

502

503 *Figure 2. Single-Unit Responses during Task Performance*

504 **A** Representative coronal section; stars indicate the estimated locations of the electrode tips.  
505 Electrodes outside of LP/pulvinar (LP/Pulv) were excluded. LGN, lateral geniculate nucleus;  
506 MGN, medial geniculate nucleus; PO, nucleus of the posterior group; SGN, suprageniculate  
507 nucleus.

508 **B** Top: Example of high-pass filtered raw trace from representative recording session. Bottom:  
509 Action potentials of two representative single units.

510 **C** Peri-event raster plots (top) and peri-event histograms of the corresponding firing rates  
511 (bottom) of two representative neurons. The unit on the left exhibited an increasing firing during  
512 the delay period, whereas the unit on the right did not show such modulation but rather increased  
513 its firing rate after stimulus onset.

514 **D** Z-score normalized population firing rate of attention-modulated (red, n=130) and non-  
515 attention-modulated units (black, n=129) in correct trials (solid lines) and in incorrect trials  
516 (dotted lines). Shaded areas indicate SEM. Attention-modulated units gradually increased their  
517 firing rate during the delay period. Both neuron types displayed a transient increase in firing rate  
518 after stimulus onset, with stronger responses in attention-modulated neurons. Shaded areas  
519 indicate standard error of the mean (SEM).

520 **E** Peri-event raster plots from all the attention-modulated (red, n = 130) and non-attention-  
521 modulated units (black, n = 129) in all correct trials. Units from each category are sorted by their  
522 mean firing rate in the delay period.

523

524 *Figure 3. Interaction of Spiking Activity and the Local Field Potential in the Theta Band*

525 **A-D** Spike-field coherence across sessions and animals for different task epochs for attention-  
526 modulated (red) and non-attention modulated units (black). A, before initiation; B, delay period  
527 (from initiation to stimulus onset); C, before touch (from stimulus onset to touch response); D,  
528 after touch. The inset in B shows the spike-triggered average of the LFP averaged across the  
529 attention-modulated (red) and non-attention-modulated units (black), and the shuffle control  
530 (green) in the 5 sec delay period for all correct trials. The vertical dashed line indicates the spike  
531 time. Shaded areas both in the spike-field coherence plots and in the spike-triggered average plot  
532 represent SEM.

533 **E** Spike-field coherence of attention-modulated and non-attention-modulated units in theta band  
534 (4-6 Hz) for different task epochs. Theta coherence was differentially modulated by task

535 performance. Attention-modulated units showed significantly higher coherence than non-  
536 attention-modulated units at all task epochs, except after touch. For attention-modulated units,  
537 theta coherence increased during the delay period compared to before trial initiation and reached  
538 the maximum before touch. No change in coherence occurred for non-attention-modulated units  
539 during the task. \* indicates  $p < 0.05$ ; NS indicates  $p > 0.05$ . Error bars represent SEM.

540

541 *Figure 4. Task-Modulated Theta-Gamma Phase Amplitude Coupling (PAC)*

542 **A** Modulation of theta power during task performance. Theta power gradually increased and was  
543 maintained during the delay period and peaked between stimulus onset and screen touch. Shaded  
544 area represents SEM. An example LFP trace (bandpass in 1-20 Hz) is displayed on the top and  
545 shows the theta oscillation throughout a trial.

546 **B** Heatmap of phase-amplitude coupling (PAC) during task performance shows selective  
547 coupling of theta and gamma oscillations. An example LFP trace (bandpass in 1-100 Hz) is  
548 superimposed on the heatmap and shows gamma-theta oscillation nesting.

549 **C** Task-dependent modulation of time-resolved theta-gamma PAC. Theta-gamma PAC was  
550 elevated throughout the delay period and decreased after screen touch. Shaded area shows SEM.

551 **D** Modulation of gamma power during task performance. Gamma power gradually decreased  
552 during the delay period. Shaded area represents SEM.

553

554 **References**

555

- 556 Bari, A., J. W. Dalley and T. W. Robbins (2008). "The application of the 5-choice serial reaction time  
557 task for the assessment of visual attentional processes and impulse control in rats." *Nat. Protocols* **3**(5):  
558 759-767.
- 559 Bari, A., J. W. Dalley and T. W. Robbins (2008). "The application of the 5-choice serial reaction time  
560 task for the assessment of visual attentional processes and impulse control in rats." *Nat Protoc* **3**(5): 759-  
561 767.
- 562 Barkley, R. A. (1997). "Behavioral inhibition, sustained attention, and executive functions: Constructing a  
563 unifying theory of ADHD." *Psychological Bulletin* **121**(1): 65-94.
- 564 Bellgrove, M. A., Z. Hawi, M. Gill and I. H. Robertson (2006). "The Cognitive Genetics of Attention  
565 Deficit Hyperactivity Disorder (ADHD): Sustained attention as a Candidate Phenotype." *Cortex* **42**(6):  
566 838-845.
- 567 Bokil, H., K. Purpura, J. M. Schoffelen, D. Thomson and P. Mitra (2007). "Comparing spectra and  
568 coherences for groups of unequal size." *J Neurosci Methods* **159**(2): 337-345.
- 569 Brainard, D. H. (1997). "The Psychophysics Toolbox." *Spat Vis* **10**(4): 433-436.
- 570 CLARK, L., S. D. IVERSEN and G. M. GOODWIN (2002). "Sustained attention deficit in bipolar  
571 disorder." *The British Journal of Psychiatry* **180**(4): 313-319.
- 572 Cohen, R. A., Y. A. Sparling-Cohen and B. F. O'Donnell (1993). *The neuropsychology of attention*. New  
573 York, Plenum Press.
- 574 Crighel, E., A. Kreindler and S. Sirian (1978). "Relations between the pulvinar-lateralis posterior complex  
575 of the thalamus and the hippocampus in wakefulness and sleep in cats." *Acta Neurobiol Exp (Wars)*  
576 **38**(4): 167-178.
- 577 Day, M., J. B. Pan, M. J. Buckley, E. Cronin, P. R. Hollingsworth, W. D. Hirst, R. Navarra, J. P. Sullivan,  
578 M. W. Decker and G. B. Fox (2007). "Differential effects of ciproxifan and nicotine on impulsivity and  
579 attention measures in the 5-choice serial reaction time test." *Biochemical Pharmacology* **73**(8): 1123-  
580 1134.
- 581 Frohlich, F. (2016). *Network neuroscience*. Boston, MA, Elsevier.
- 582 Johnson, K. A., I. H. Robertson, S. P. Kelly, T. J. Silk, E. Barry, A. Dáibhis, A. Watchorn, M. Keavey,  
583 M. Fitzgerald, L. Gallagher, M. Gill and M. A. Bellgrove (2007). "Dissociation in performance of  
584 children with ADHD and high-functioning autism on a task of sustained attention." *Neuropsychologia*  
585 **45**(10): 2234-2245.
- 586 Jones, E. G. (2007). *The thalamus*. Cambridge ; New York, Cambridge University Press.
- 587 Kaas, J. H. (2007). "The thalamus revisited: where do we go from here?" *Brain* **130**(9): 2470-2473.
- 588 Lewin, J. S., L. Friedman, D. Wu, D. A. Miller, L. A. Thompson, S. K. Klein, A. L. Wise, P. Hedera, P.  
589 Buckley, H. Meltzer, R. P. Friedland and J. L. Duerk (1996). "Cortical Localization of Human Sustained  
590 Attention: Detection with Functional MR Using a Visual Vigilance Paradigm." *Journal of Computer*  
591 *Assisted Tomography* **20**(5): 695-701.
- 592 Llinas, R. R. and M. Steriade (2006). "Bursting of thalamic neurons and states of vigilance." *J*  
593 *Neurophysiol* **95**(6): 3297-3308.
- 594 Martínez-Arán, A., E. Vieta, F. Colom, M. Reinares, A. Benabarre, C. Gastó and M. Salamero (2000).  
595 "Cognitive Dysfunctions in Bipolar Disorder: Evidence of Neuropsychological Disturbances."  
596 *Psychotherapy and Psychosomatics* **69**(1): 2-18.
- 597 Mirsky, A. F., B. J. Anthony, C. C. Duncan, M. B. Ahearn and S. G. Kellam (1991). "Analysis of the  
598 elements of attention: A neuropsychological approach." *Neuropsychology Review* **2**(2): 109-145.
- 599 Paelecke-Habermann, Y., J. Pohl and B. Lepow (2005). "Attention and executive functions in remitted  
600 major depression patients." *Journal of Affective Disorders* **89**(1): 125-135.

- 601 Ramcharan, E. J., J. W. Gnadt and S. M. Sherman (2005). "Higher-order thalamic relays burst more than  
602 first-order relays." *Proceedings of the National Academy of Sciences of the United States of America*  
603 **102**(34): 12236-12241.
- 604 Riccio, C. A., C. R. Reynolds, P. Lowe and J. J. Moore (2002). "The continuous performance test: a  
605 window on the neural substrates for attention?" *Archives of Clinical Neuropsychology* **17**(3): 235-272.
- 606 Robbins, T. (2002). "The 5-choice serial reaction time task: behavioural pharmacology and functional  
607 neurochemistry." *Psychopharmacology* **163**(3): 362-380.
- 608 Ronald Cohen, Ilan Lohr, Robert Paul and Robert Boland (2001). "Impairments of Attention and Effort  
609 Among Patients With Major Affective Disorders." *The Journal of Neuropsychiatry and Clinical*  
610 *Neurosciences* **13**(3): 385-395.
- 611 Saalmann, Yuri B. and S. Kastner "Cognitive and Perceptual Functions of the Visual Thalamus." *Neuron*  
612 **71**(2): 209-223.
- 613 Saalmann, Y. B., M. A. Pinsk, L. Wang, X. Li and S. Kastner (2012). "The pulvinar regulates information  
614 transmission between cortical areas based on attention demands." *Science* **337**(6095): 753-756.
- 615 Saalmann, Y. B., M. A. Pinsk, L. Wang, X. Li and S. Kastner (2012). "The Pulvinar Regulates  
616 Information Transmission Between Cortical Areas Based on Attention Demands." *Science* **337**(6095):  
617 753-756.
- 618 Sarter, M., B. Givens and J. P. Bruno (2001). "The cognitive neuroscience of sustained attention: where  
619 top-down meets bottom-up." *Brain Research Reviews* **35**(2): 146-160.
- 620 Schmitt, L. I., R. D. Wimmer, M. Nakajima, M. Happ, S. Mofakham and M. M. Halassa (2017).  
621 "Thalamic amplification of cortical connectivity sustains attentional control." *Nature* **advance online**  
622 **publication**.
- 623 Sellers, K. K., C. Yu, Z. C. Zhou, I. Stitt, Y. Li, S. Radtke-Schuller, S. Alagapan and F. Frohlich (2016).  
624 "Oscillatory Dynamics in the Frontoparietal Attention Network during Sustained Attention in the Ferret."  
625 *Cell Rep* **16**(11): 2864-2874.
- 626 Shi K. Liu, Chia-Hui Chiu, Ching-Jui Chang, Tzung-Jeng Hwang, Hai-Gwo Hwu and Wei J. Chen  
627 (2002). "Deficits in Sustained Attention in Schizophrenia and Affective Disorders: Stable Versus State-  
628 Dependent Markers." *American Journal of Psychiatry* **159**(6): 975-982.
- 629 Shoham, S., M. R. Fellows and R. A. Normann (2003). "Robust, automatic spike sorting using mixtures  
630 of multivariate t-distributions." *J Neurosci Methods* **127**(2): 111-122.
- 631 Stitt, I., Z. C. Zhou, S. Radtke-Schuller and F. Frohlich (2017). "Arousal Dependent Modulation Of  
632 Thalamo-Cortical Functional Interaction." *bioRxiv*.
- 633 Sweeney-Reed, C. M., T. Zaehle, J. Voges, F. C. Schmitt, L. Buentjen, V. Borchardt, M. Walter, H.  
634 Hinrichs, H.-J. Heinze, M. D. Rugg and R. T. Knight (2017). "Anterior Thalamic High Frequency Band  
635 Activity Is Coupled with Theta Oscillations at Rest." *Frontiers in Human Neuroscience* **11**(358).
- 636 Sweeney-Reed, C. M., T. Zaehle, J. Voges, F. C. Schmitt, L. Buentjen, K. Kopitzki, C. Esslinger, H.  
637 Hinrichs, H.-J. Heinze, R. T. Knight and A. Richardson-Klavehn (2014). "Corticothalamic phase  
638 synchrony and cross-frequency coupling predict human memory formation." *eLife* **3**: e05352.
- 639 Sweeney-Reed, C. M., T. Zaehle, J. Voges, F. C. Schmitt, L. Buentjen, K. Kopitzki, H. Hinrichs, H.-J.  
640 Heinze, M. D. Rugg, R. T. Knight and A. Richardson-Klavehn (2015). "Thalamic theta phase alignment  
641 predicts human memory formation and anterior thalamic cross-frequency coupling." *eLife* **4**: e07578.
- 642 Tsanov, M., E. Chah, N. Wright, S. D. Vann, R. Reilly, J. T. Erichsen, J. P. Aggleton and S. M. O'Mara  
643 (2011). "Oscillatory Entrainment of Thalamic Neurons by Theta Rhythm in Freely Moving Rats." *Journal*  
644 *of Neurophysiology* **105**(1): 4-17.
- 645 Wimmer, R. D., L. I. Schmitt, T. J. Davidson, M. Nakajima, K. Deisseroth and M. M. Halassa (2015).  
646 "Thalamic control of sensory selection in divided attention." *Nature* **526**(7575): 705-709.
- 647 Yu, C., K. K. Sellers, S. Radtke-Schuller, J. Lu, L. Xing, V. Ghukasyan, Y. Li, Y. I. Shih, R. Murrow and  
648 F. Frohlich (2015). "Structural and Functional Connectivity between the Lateral Posterior-Pulvinar  
649 Complex and Primary Visual Cortex in the Ferret." *Eur J Neurosci*.

- 650 Yu, C., K. K. Sellers, S. Radtke-Schuller, J. Lu, L. Xing, V. Ghukasyan, Y. Li, Y. Y. Shih, R. Murrow  
651 and F. Fröhlich (2016). "Structural and functional connectivity between the lateral posterior-pulvinar  
652 complex and primary visual cortex in the ferret." *Eur J Neurosci* **43**(2): 230-244.
- 653 Yu, C. X., K. K. Sellers, S. Radtke-Schuller, J. H. Lu, L. Xing, V. Ghukasyan, Y. H. Li, Y. Y. I. Shih, R.  
654 Murrow and F. Fröhlich (2016). "Structural and functional connectivity between the lateral posterior-  
655 pulvinar complex and primary visual cortex in the ferret." *European Journal of Neuroscience* **43**(2): 230-  
656 244.
- 657 Zhou, H., Robert J. Schafer and R. Desimone "Pulvinar-Cortex Interactions in Vision and Attention."  
658 *Neuron* **89**(1): 209-220.
- 659 Zhou, Z. C., A. P. Salzwedel, S. Radtke-Schuller, Y. Li, K. K. Sellers, J. H. Gilmore, Y. I. Shih, F.  
660 Fröhlich and W. Gao (2016). "Resting state network topology of the ferret brain." *Neuroimage* **143**: 70-  
661 81.
- 662 Zhou, Z. C., C. Yu, K. K. Sellers and F. Fröhlich (2016). "Dorso-Lateral Frontal Cortex of the Ferret  
663 Encodes Perceptual Difficulty during Visual Discrimination." **6**: 23568.

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