

1 Top-down coordination of local cortical 2 state during selective attention

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12 Abstract:

13 Spontaneous fluctuations in cortical excitability influence sensory processing and behavior.
14 These fluctuations, long known to reflect global changes in cortical state, were recently
15 found to be modulated locally within a retinotopic map during spatially selective attention.
16 We found that periods of vigorous (On) and faint (Off) spiking activity, the signature of
17 cortical state fluctuations, were coordinated across brain areas along the visual hierarchy
18 and tightly coupled to their retinotopic alignment. During top-down attention, this
19 interareal coordination was enhanced and progressed along the reverse cortical hierarchy.
20 The extent of local state coordination between areas was predictive of behavioral
21 performance. Our results show that cortical state dynamics are shared across brain regions,
22 modulated by cognitive demands and relevant for behavior.

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24 One Sentence Summary:

25 Interareal coordination of local cortical state is retinotopically precise and progresses in a
26 reverse hierarchical manner during selective attention.

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28 Main Text:

29 Cortical activity is not solely determined by external inputs but reflects ongoing fluctuations
30 in neural excitability referred to as cortical state (Harris and Thiele, 2011; Kohn et al., 2009).
31 Endogenous variability in cortical state shapes sensory responses and influences behavioral
32 performance (Arieli et al., 1996; Gutnisky et al., 2017; McGinley et al., 2015a; Renart and
33 Machens, 2014; Scholvinck et al., 2015). Although these fluctuations were long thought to
34 be a global phenomenon that influences activity throughout the cortex (Harris and Thiele,
35 2011; Lee and Dan, 2012), recent evidence has revealed that signatures of cortical state are
36 modulated locally within the retinotopic map in Macaque V4 during selective attention
37 (Engel et al., 2016). Cortical state fluctuations manifest in periods of vigorous (On) and faint
38 (Off) spiking activity occurring synchronously across cortical laminae. Spatially selective
39 attention directed towards the receptive fields (RFs) of the neural population modulates On-
40 Off dynamics by increasing the duration of On episodes (Engel et al., 2016). Thus, cognitive
41 demands that selectively affect targeted retinotopic locations can modulate local signatures
42 of global cortical state fluctuations. However, perception and cognition depend on activity
43 of many areas spanning the cortical hierarchy, which begs the question of whether cortical-
44 state dynamics are coordinated across different brain regions during attention, whether this
45 coordination progresses in a top-down or bottom-up manner, and whether it is relevant for
46 behavior.

47 We recorded simultaneously from V1 and V4 using 16-contact laminar electrodes whilst
48 three rhesus macaques performed a feature-based spatial attention task (Fig. 1A).
49 Electrodes were inserted perpendicular to the cortical surface on a daily basis such that RFs
50 overlapped both across all channels within each area and between the two areas (Fig. 1B &
51 Fig. 1C). We characterized On-Off dynamics in each area individually by fitting a Hidden
52 Markov Model (HMM) to the spike counts (10 ms bins) of multiunit activity (MUA) across
53 included channels (supplementary material, Fig. 1D). In line with previous reports for V4
54 (Engel et al., 2016), we found that a 2-phase model was the most parsimonious model for
55 the majority of recordings (V1: 64 out of 77 recordings (83.1%), V4: 73 out of 79 recordings
56 (92.4%), V1 and V4: 57 out of 73 recordings (78.1%), Fig. S1A-D). During these recordings,
57 On-Off dynamics occurred without any obvious periodicity (Fig. S1E). When attention was
58 directed towards the RFs under study, firing rates were higher during both Off and On

59 epochs [Wilcoxon signed rank test; V1: Off $P = 10^{-164}$, On $P = 10^{-87}$, V4: Off $P = 10^{-184}$, On $P =$
60 10^{-103}] (Fig. 1E), On-epoch durations increased in both V1 and V4 [Wilcoxon signed rank test;
61 V1 $P = 10^{-13}$, V4 $P = 10^{-8}$] and Off epoch durations increased in V1 but not V4 [Wilcoxon
62 signed rank test; V1: $P = 10^{-8}$, V4 $P = 0.81$] (Fig. 1F). Additionally, when attention was
63 directed towards the RFs, altogether more time was spent in an On phase (Fig. S2A) and
64 transitions to an On phase were more likely (Fig. S2B).

65 We examined whether these spontaneous transitions were coordinated across visual areas.
66 We computed cross-correlations between the V1 and V4 time series of On-Off phases (as
67 estimated by the HMMs) during passive fixation (before stimulus onset) and during directed
68 attention (after cue onset). During fixation, V1 and V4 transitions were coordinated but
69 without either area leading/lagging the other [Wilcoxon signed rank test; $P = 0.13$] (Fig. 2A).
70 During directed attention, the coordination between V1 and V4 was enhanced and On-Off
71 transitions more often occurred in V4 before they were followed in V1, as evident from the
72 skew towards negative values of the V4 relative to V1 transition times [Wilcoxon signed
73 rank test; $P < 10^{-5}$] (Fig. 2A). The cross-correlation strength and skew was independent of
74 microsaccades (Fig. S3), and the strength was inversely related to the separation between
75 V1 and V4 RFs [$r = -0.38$, $P = 0.004$] (Fig. 2B). Thus, the strength of On-Off dynamics
76 coordination between visual areas is tightly coupled to their retinotopic alignment. To
77 further characterize this interareal coordination, we computed average firing rates in V1
78 aligned to On-Off transition times in V4 and vice-versa. In line with transitions being driven
79 in a top-down manner, V1 firing rate changes followed V4 transitions whereas V4 firing rate
80 changes preceded V1 transitions (Fig. 2C). We also analyzed spiking activity simultaneously
81 recorded with 16-contact linear electrodes inserted perpendicular to layers in V4 and
82 tangential to layers in the frontal eye field (FEF) (or with single electrodes in FEF in some
83 sessions) from two monkeys performing a selective attention task (V4 data reported
84 previously in ref. (Engel et al., 2016)). A similar analysis revealed that changes of FEF firing
85 rates precede On-Off transitions in V4 (Fig. 2D). These results suggest that On-Off transitions
86 traverse from higher to lower areas along the visual hierarchy during selective attention.

87 To investigate the relationship between V1 and V4 On-Off transitions more closely, we fit a
88 4-state HMM to V1 and V4 data simultaneously (HMM_{V1-V4}), with the four HMM-states
89 defined as (state 1) V1_{off}-V4_{off}, (state 2) V1_{on}-V4_{off}, (state 3) V1_{off}-V4_{on} and (state 4) V1_{on}-V4_{on}

90 (Fig. 3A). This model allowed us to investigate two specific scenarios (Fig. 3B). In the first
91 scenario (yellow), we asked: from a situation in which both areas are in an Off phase (state
92 1), is it more likely for V1 (state 2) or V4 (state 3) to transition (first) to an On phase? The
93 second scenario (purple) addresses a related question: from a situation in which both areas
94 are in an On phase (state 4), is it more likely for V1 (state 3) or V4 (state 2) to transition
95 (first) to an Off state? The transition probabilities (Fig. 3C & Fig. 3D) revealed that when
96 both areas were in an Off phase, it was more likely for V4 to transition to an On phase first
97 [Wilcoxon signed rank test; $P < 10^{-3}$]. Likewise, if both areas were in an On phase, it was
98 more likely for V4 to transition to an Off phase first [Wilcoxon signed rank test; $P < 10^{-3}$].
99 Thus, when both areas are in the same phase, it is more likely for V4 to transition away from
100 this phase first. This finding was, however, not specific to the attend RF condition, as we
101 found similar results for each individual attention condition (attend RF and attend away), as
102 well as during fixation (data not shown). Selective attention, however, modulated the
103 transition probabilities from the yellow scenario. Specifically, it decreased the probability of
104 transitioning from state 1 to state 2, and increased the probability of transitioning from
105 state 1 to state 3 [Wilcoxon signed rank test; $P < 10^{-2}$] (Fig. 3E & Fig. 3F). Finally, this model
106 revealed that, although On-Off phases/transitions are correlated, each area spends a
107 substantial fraction of time in opposite phases (Fig. 3G). Selective attention specifically
108 decreases the time spent in state 1 whereas it increases the time spent in state 3 and state
109 4, i.e. the states where V4 was in an On phase [Wilcoxon signed rank test; state 1 $P < 10^{-5}$,
110 state 2 $P = 0.91$, state 3 $P < 10^{-2}$, state 4 $P < 10^{-3}$] (Fig. 3H).

111 On-Off dynamics furthermore related closely to measures of (bipolar re-referenced) local
112 field potential (LFP) (de)synchronization. During On phases in either V1 or V4, low frequency
113 ($< \sim 20$ Hz) LFP power was suppressed and high frequency ($> \sim 20$ Hz) power was increased,
114 both in V1 and V4 (Fig. S4A-D). Additionally, LFP power spectra in both areas varied across
115 the 4 states of HMM_{V1-V4} (Fig. S4E-F). Here, we specifically investigated the difference in
116 power spectra across states where the On-Off phase within an area remained constant, but
117 differed in the other area. For example, we investigated the V1 LFP power spectra across
118 states 1 and 3, wherein V1 was in an Off phase during both states, but V4 was either Off or
119 On. This analysis revealed that the LFP power in V1 is modulated by V4 phase
120 bidirectionally. If V1 was in either an On or an Off phase, a transition to an On phase in V4

121 increased V1 high-frequency power. A transition to an On phase in V1, however, only
122 affected V4 high-frequency power when V4 was in an Off phase. When V4 was in an On
123 phase, V1 phase did not affect high-frequency dynamics in V4. Thus, V4 phase influenced V1
124 LFP regardless of V1 phase, whereas V1 phase affected high-frequency dynamics in V4 only
125 during Off phases in V4.

126 In addition to selective attention, On-Off dynamics were linked to global arousal levels, as
127 measured by pupil diameter (Aston-Jones and Cohen, 2005; McGinley et al., 2015a, 2015b;
128 Reimer et al., 2014; Vinck et al., 2015). For each area individually, On epoch durations were
129 longer on trials with larger baseline pupil diameter (Fig. S5A-C), in line with previous results
130 (Engel et al., 2016). Furthermore, pupil diameter was predictive of On-Off dynamics
131 coordination. Larger baseline pupil diameter was predictive of shorter epoch durations for
132 HMM_{V1-V4} state 1 (where both areas were Off) and longer state 4 epoch durations (where
133 both areas were On) (Fig. S5D). Central arousal, in addition to focused attention, thus
134 specifically influenced epoch durations for states where V1 and V4 phase were aligned.
135 Importantly, pupil diameter did not differ between attention conditions (Fig. S5E), while
136 cortical state did. This shows that effects of arousal and attention on On-Off dynamics are
137 independently controlled.

138 We have demonstrated that the coordination of On-Off dynamics is retinotopically
139 organized and driven in a top-down manner during selective attention. Is this organization
140 also relevant for behavior? For both V1 and V4 individually, the On/Off phase at the time of
141 target dimming was predictive of reaction time (RT) when the target was presented inside
142 the RFs. We found an interaction between attention and On/Off phase [linear mixed effects
143 model; V1 $\beta = 0.16 \pm 0.06$, $P = 0.006$, V4 $\beta = 0.13 \pm 0.06$, $P = 0.03$] with a main effect for phase
144 [V1 $\beta = -0.27 \pm 0.09$, $P = 0.002$, V4 $\beta = -0.26 \pm 0.09$, $P = 0.004$], but no main effect of attention
145 [V1 $\beta = -0.15 \pm 0.09$, $P = 0.09$, V4 $\beta = -0.1 \pm 0.09$, $P = 0.28$]. Specifically, when either area was in
146 an On phase when the target grating dimmed, RT was faster [Wilcoxon signed rank test; V1
147 $P = 0.001$, V4 $P < 10^{-4}$] (Fig. 4A). We furthermore found that On-Off phase coordination
148 between V1 and V4, as assessed using HMM_{V1-V4} , was also predictive of behavioral
149 performance. Again we found an interaction between attention and On/Off phase [linear
150 mixed effects model; $\beta = 0.08 \pm 0.02$, $P < 10^{-3}$], with a main effect of phase [$\beta = -0.15 \pm 0.04$, P
151 $< 10^{-4}$], but not of attention [$\beta = -0.07 \pm 0.07$, $P = 0.24$]. Performance was worst when at the

152 time of target dimming both V1 and V4 were in an Off phase (state 1). Performance
153 improved when either area was in an On phase, and it improved even further when both
154 areas were in an On phase at the time of target dimming (Fig. 4B). The coordination of On-
155 Off dynamics across visual areas is thus more beneficial for behavioral performance than the
156 state in either area alone.

157 In line with previous results (Engel et al., 2016), we show that transitions between On and
158 Off phases in V4 are modulated locally by spatially selective attention. In addition, we found
159 that they also occur in primary visual cortex (V1). Importantly, we show that interareal
160 coordination of On-Off dynamics occurs at a local retinotopic scale, which reflects the
161 precision of anatomical connections, and is driven in a top-down manner across areas FEF,
162 V4 and V1 during selective attention. Fluctuations in cortical state have previously been
163 ascribed to neuromodulatory influences (Buzsaki et al., 1988; Constantinople and Bruno,
164 2011; Lee and Dan, 2012) and feedback projections (Zagha et al., 2013). On-Off dynamics
165 relate to both these mechanisms as pupil diameter, associated with neuromodulatory
166 regulation of network state (Aston-Jones and Cohen, 2005; de Gee et al., 2017; Eldar et al.,
167 2013; Joshi et al., 2016; Murphy et al., 2014; Reimer et al., 2016; Varazzani et al., 2015), and
168 top-down retinotopic alignment, probably driven by feedback mechanisms (Zagha et al.,
169 2013), are predictive of cortical state fluctuations.

170 The interareal coordination of On-Off dynamics and its relevance to behavioral performance
171 suggests that trial-by-trial coordination of activity across brain regions is beneficial for
172 information transfer and selectively modulated according to task demands. Across-area
173 oscillatory activity is correlated according to both retinotopy and stimulus selectivity (Lewis
174 et al., 2016). Selective attention modulates this interareal coherence (Bosman et al., 2012;
175 Buschman and Miller, 2007; Gregoriou et al., 2009), potentially facilitating communication
176 between hierarchically linked areas (Fries, 2005). Although attention can reduce within-area
177 spike count correlations (Cohen and Maunsell, 2009; Herrero et al., 2013; Mitchell et al.,
178 2009), depending on the signal correlation between neuronal pairs (Rabinowitz et al., 2015;
179 Ruff and Cohen, 2014), it increases correlated variability across functionally related areas
180 (Oemisch et al., 2015; Ruff and Cohen, 2016). This increased coordination might be a
181 prerequisite for successful interareal information transfer (Harris and Mrsic-Flogel, 2013)
182 and might allow propagation of sensory information to other brain regions (Luczak et al.,

183 2013). When hierarchically linked areas are simultaneously active, potentially driven by the
184 frontal cortex, global representation of information through recurrent processing could be
185 facilitated, thereby aiding conscious stimulus processing (Baars, 2002; Dehaene and
186 Changeux, 2011). Cognitive modulation of cortical state coordination could be a key
187 component of this.

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347 Supervision

348 Alexander Thiele: Conceptualization, Investigation, Resources, Writing – review and editing,
349 Supervision, Funding acquisition

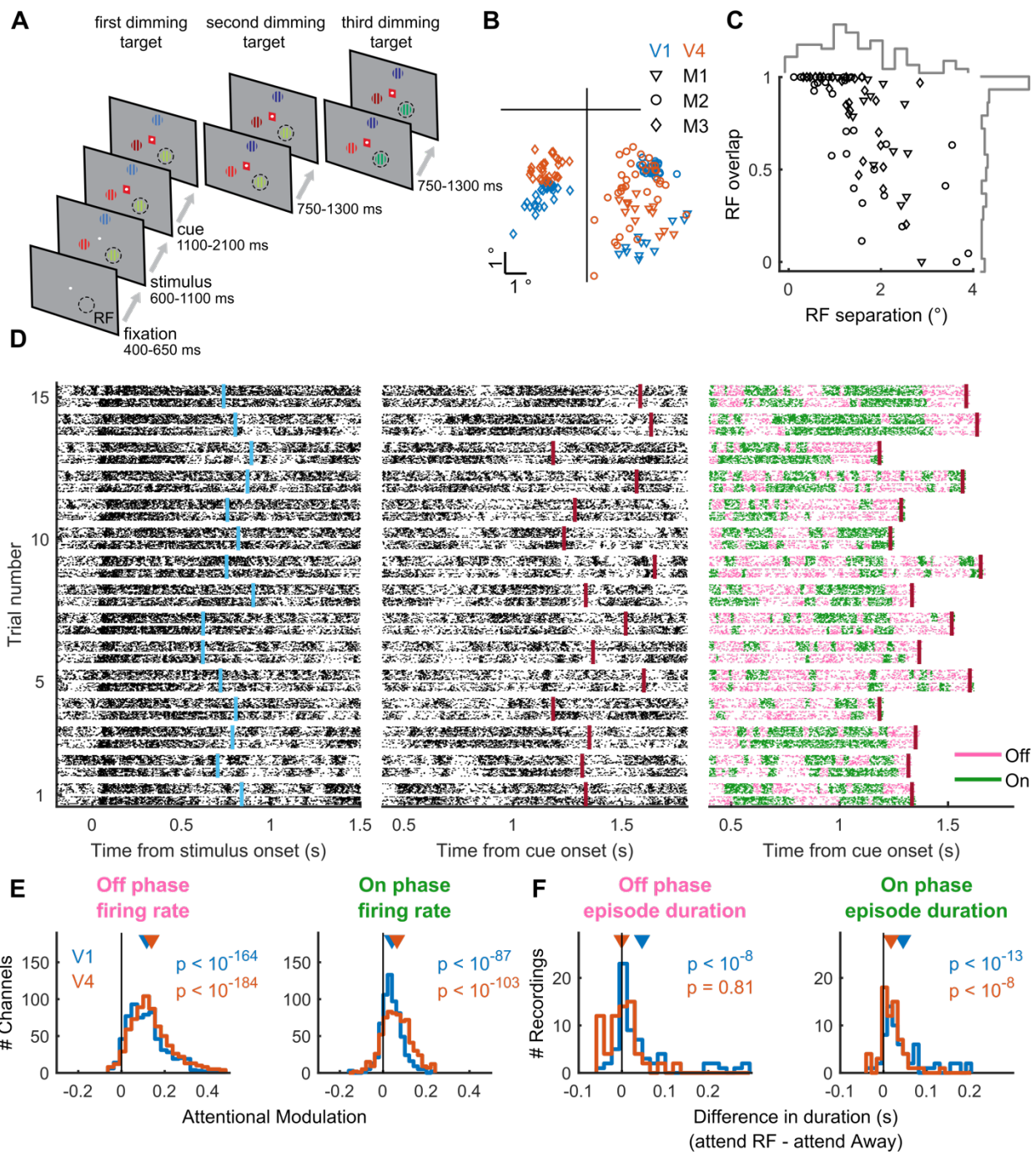
350 [Competing interests:](#)

351 There are no competing interests.

352 [Data and materials availability:](#)

353 Data and materials are available upon request.

354



355

356 **Fig. 1. On-Off dynamics in V1 and V4 are modulated during selective attention. (A)**

357 Behavioral paradigm. The monkey held a lever to initiate the trial, hereafter a central

358 fixation spot was turned on. Upon fixation 3 colored gratings appeared, one was presented

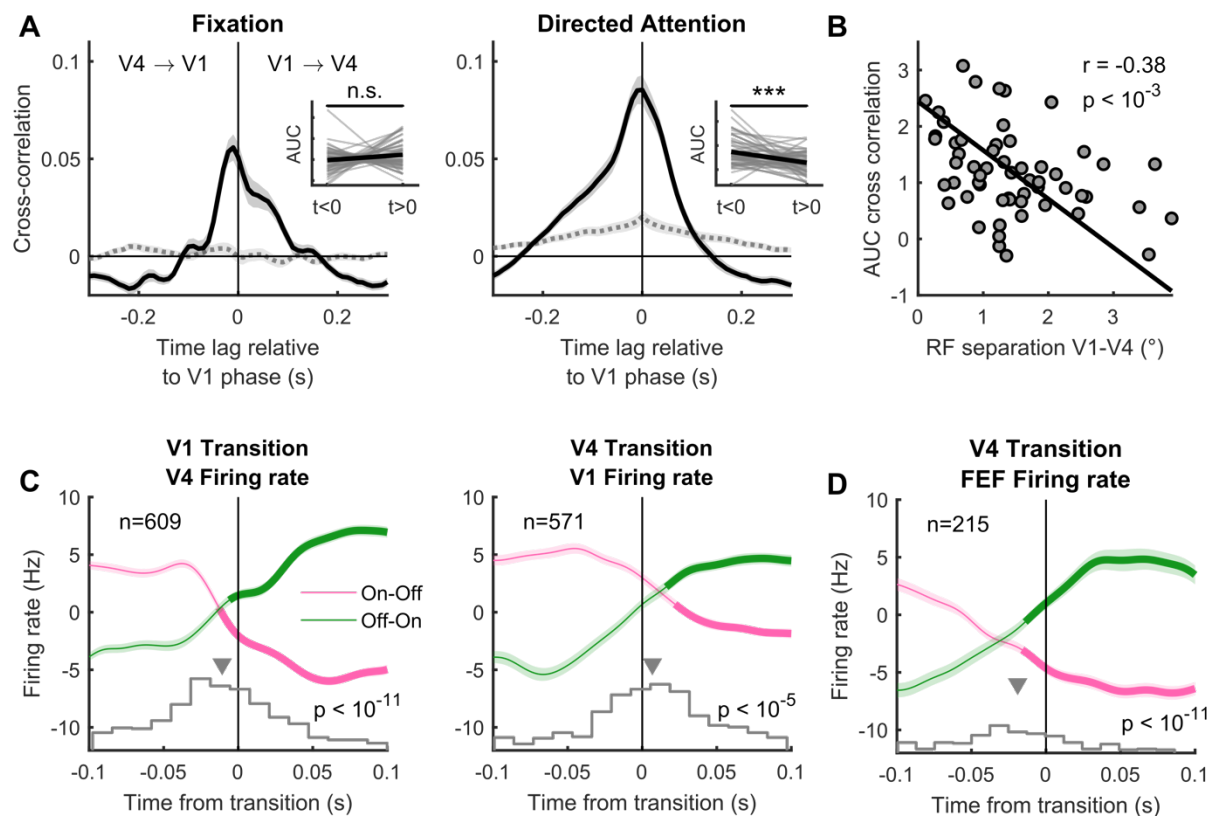
359 inside the receptive fields (RFs) of the V1 neurons. After a variable delay a cue matching one

360 of the grating colors surrounded the fixation spot, indicating which grating was behaviorally

361 relevant (target). In pseudorandom order the stimuli decreased in luminance (dimmed).

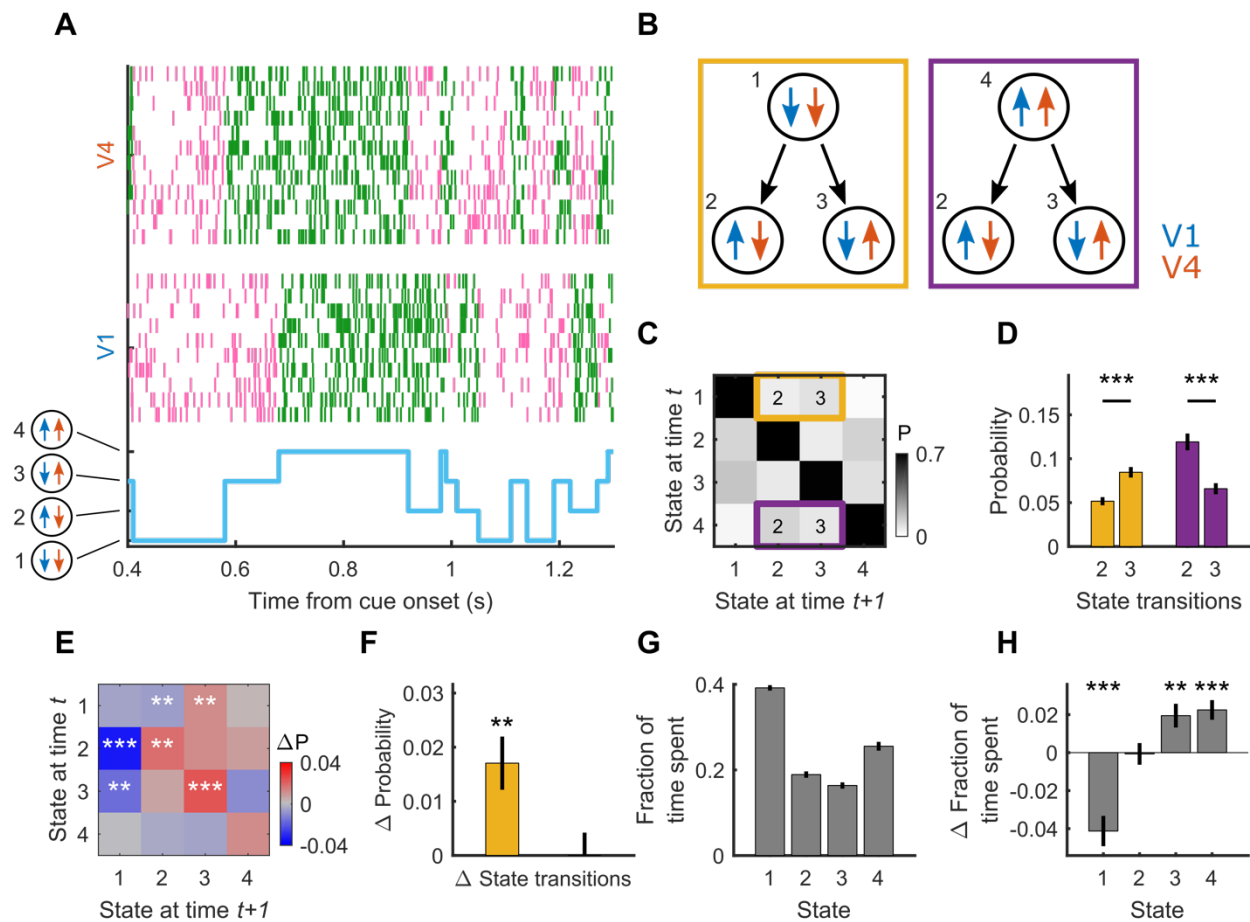
362 Upon dimming of the target, the monkey had to release the lever. (B) Average RF center

363 locations (across channels) for each recording, separately for each subject (M1-M3) and
364 area. **(C)** RF separation between V1 and V4 plotted against their overlap, expressed as the
365 proportion of the V1 RF. The histograms along the top (right) indicate the distribution of RF
366 separation (overlap) across all recordings. **(D)** Raster plot of HMM fit to population activity
367 in V1 and V4. Simultaneously recorded multi-unit spiking activity on 16-contact laminar
368 electrodes in V1 and V4 for 15 example trials, aligned to stimulus (left) and cue onset
369 (middle and right). Each trial shows across laminar activity in V1 (bottom) and V4 (top), as
370 raster plots (left two columns) color coded according to HMM estimation of On and Off
371 phases (right). Middle and right columns depict the same activity. The HMM was fit from
372 400 ms after cue onset to 30 ms after the first dimming event. Cue onset and first-dimming
373 are indicated for each trial by purple and red vertical bars respectively. **(E)** Attention
374 increases firing rates during Off and On phases, both in V1 and V4. **(F)** Attention increases
375 the duration of On episodes, both in V1 and V4, whereas it increases the duration of Off
376 episodes only in V1. Statistics: Wilcoxon signed rank test.



377

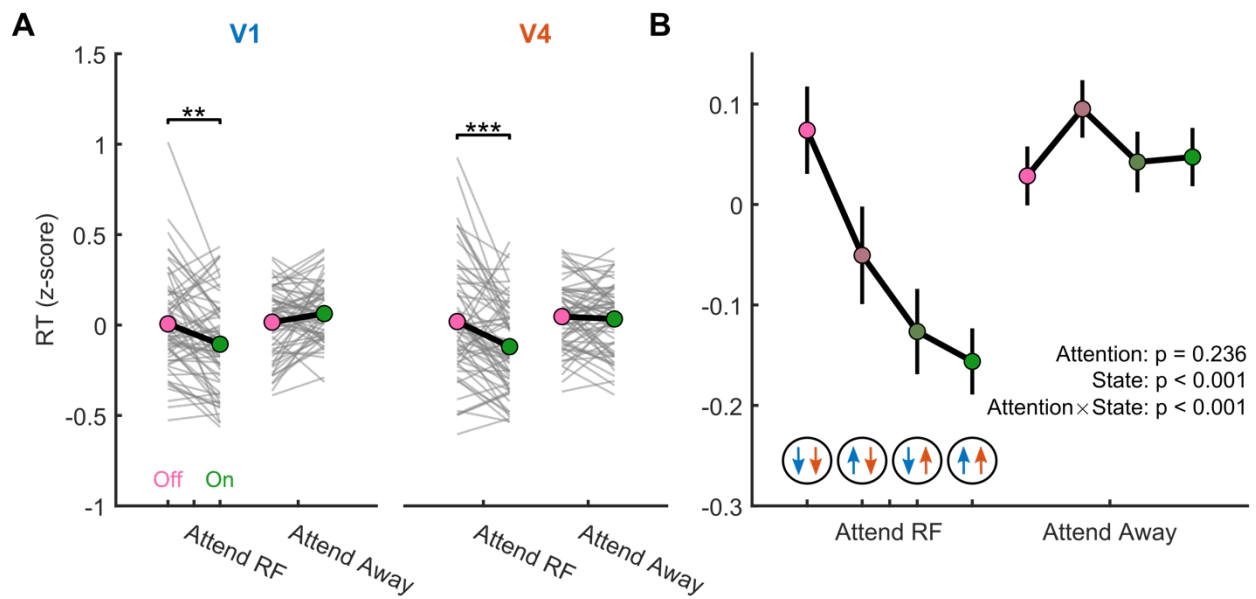
378 **Fig. 2. Across area coordination of cortical state.** (A) Cross-correlation between time series
 379 of On-Off phases in V1 and V4 relative to V1 phase during passive fixation (left) and after
 380 cue onset (right). Insets show the area under the cross-correlation curve for times smaller
 381 and larger than zero. The dashed grey line depicts the shuffle predictor. (B) RF separation
 382 plotted against the area under the cross-correlation curve during attention (from the right
 383 panel A). The line indicates the standardized major axis regression fit. (C) Spiking activity in
 384 one area aligned to state transitions in the other area, averaged across channels and
 385 recordings. Only epochs without transitions preceding or following the alignment transition
 386 within 100 ms were included. Thick green and pink lines indicate the times the firing rate
 387 was higher (green) or lower (pink) than the average rate. Along the bottom are the
 388 histograms of the crossing point of two straight lines fit (least-squares) to the transition-
 389 aligned multi-unit firing rate. (D) Conventions as in C, but from a different dataset in which
 390 activity was recorded simultaneously from V4 and FEF. Statistics: Wilcoxon signed rank test
 391 (A), Pearson correlation (B) and FDR-corrected, one-sided, Wilcoxon signed rank test (C &
 392 D). Shaded regions denote ±1 SEM.



393

394 **Fig. 3. HMM with 4 states fit simultaneously to V1 and V4 data.** (A) Example trial with the
 395 HMM state-trajectory (bottom) and across-laminar raster plot for V1 (middle) and V4 (top).
 396 (B) Schematic describing scenarios for testing two questions: (1, left yellow box) from a
 397 state where both V1 and V4 are Off, is it more likely for V1 or V4 to transition to the On
 398 phase first? (2, right purple box) from a state where both V1 and V4 are On, is it more likely
 399 for V1 or V4 to transition to the Off phase first? (C) HMM transition probability matrix,
 400 indicating the probability of staying in a state (diagonal) or transitioning from one state to
 401 another. Highlighted are scenarios set out in panel B. (D) Transition probabilities indicated in
 402 panels B and C. (E) Attentional influence on state-transition probabilities: shown is the
 403 difference transition matrix (attend RF – attend Away). (F) Attentional influence (attend RF –
 404 attend Away) on the difference between state transition probabilities (state 3 – state 2) for
 405 each of the two scenarios indicated in panels B, C and D. Selective attention increases the
 406 difference between the transition probabilities for state 2 and 3 for the yellow, but not the
 407 purple scenario. (G) The fraction of time spent in each of the 4 states. (H) The difference in

408 time spent in each of the 4 states when attention is directed towards or away from the RF
409 (attend RF – attend Away). Statistics: Wilcoxon signed rank test (FDR corrected), error bars
410 denote ± 1 SEM across recordings; *, **, *** indicate significance levels ($p < 0.05$, $p < 0.01$
411 and $p < 0.001$, respectively).



412

413 **Fig. 4. Across-area coordination of On-Off dynamics predicts behavioral performance. (A)**

414 On vs. Off phase of population activity at the time of target dimming, determined

415 individually for V1 and V4, predicts behavioral performance. RT decreases when attention is

416 directed towards the RFs and either V1 or V4 is in an On phase. (B) RT decreased from when

417 both areas were Off, through V1 On - V4 Off, through V1 Off - V4 On, to V1 and V4 On when

418 attention was directed towards the RFs. Statistics: Wilcoxon signed rank test (A), and

419 multilevel linear mixed effect model (B). Error bars denote ± 1 SEM, and *, ** and ***

420 indicate FDR corrected significance levels of $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively.

421

422 Materials and Methods

423 Animals and procedures

424 Subjects in our study were 3 male rhesus macaque monkeys (*Macaca mulatta*, age 10-12
425 years, weight 8.5-12.5 kg). All animal procedures were performed in accordance with the
426 European Communities Council Directive RL 2010/63/EC, the National Institute of Health's
427 Guidelines for the Care and Use of Animals for Experimental Procedures, and the UK
428 Animals Scientific Procedures Act. Animals were motivated to engage in the task through
429 fluid control at levels that do not affect animal physiology and have minimal impact on
430 psychological wellbeing (Gray et al., 2016).

431

432 Surgical preparation

433 The animals were implanted with a head post and recording chambers over area V1 and V4
434 under sterile conditions and general anesthesia. Surgical procedures and postoperative care
435 conditions have been described in detail previously (Thiele et al., 2006).

436

437 Behavioral paradigm

438 Stimulus presentation and behavioral control was regulated by Remote Cortex 5.95
439 (Laboratory of Neuropsychology, National Institute for Mental Health, Bethesda, MD).
440 Stimuli were presented on a cathode ray tube (CRT) monitor at 120 Hz, 1280 × 1024 pixels,
441 at a distance of 54 cm. The location and size of receptive field (RF) were measured as
442 described previously (Gieselmann and Thiele, 2008), using a reverse correlation method.
443 Briefly, during fixation, a series of black squares (0.5-2° size, 100% contrast) were presented
444 for 100 ms at pseudorandom locations on a 9 × 12 grid (5-25 repetitions for each location)
445 on a bright background. RF eccentricity ranged from 3.4 - 7.5° in V1, and from 2.5 to 8.9° in
446 V4.

447 During the main task (Fig. 1A), the monkeys initiated a trial by holding a lever and fixating on
448 a central white fixation spot (0.1°) displayed on a gray background (1.41 cd/m²). After a
449 fixed delay (614, 424, 674 ms, for monkeys 1, 2 and 3), three colored (for color values see
450 Table S1) square wave gratings appeared equidistant from the fixation spot, one was

451 centered on the RF of the V1 neurons under study. The locations of colored gratings were
452 fixed for each recording session but were pseudorandomly assigned across sessions.
453 Stimulus size varied between 2 and 4° diameter, depending on RF eccentricity and size. For
454 most recordings we used drifting gratings but presented one monkey with stationary
455 gratings during 22 out of 34 recording days. The drifting gratings moved perpendicular to
456 the grating orientation, with the motion direction pseudorandomly assigned on every trial.
457 After a random delay (618-1131 ms for monkey 1, 618-948 ms for monkeys 2 and 3;
458 uniformly distributed), a central cue appeared that matched the color of one of the gratings,
459 indicating that this grating would be behaviorally relevant on the current trial. After a
460 variable delay (1162-2133 ms for monkey 1, 1162-1822 ms for monkeys 2 and 3; uniformly
461 distributed), one of the pseudorandomly selected gratings changed luminance (for color
462 values see Table S1), referred to as dimming. If the cued grating (target) dimmed, the
463 monkey had to release the lever in order to obtain a reward. If, however, a non-cued grating
464 (distractor) dimmed, the monkey had to ignore this and keep hold of the lever until the
465 target dimmed on the second or third dimming event (each after another 792-1331 ms for
466 monkey 1; 792-1164 ms for monkeys 2 and 3; uniformly distributed).

467

468 [Data acquisition and analysis](#)

469 We recorded from all cortical layers of visual areas V1 and V4 using 16-contact laminar
470 electrodes (150 µm contact spacing, Atlas silicon probes). Out of a total of 77 V1 and 79 V4
471 recording sessions, 73 recordings were conducted simultaneously in both areas. The
472 electrodes were inserted perpendicular to the cortex on a daily basis.

473 Raw data were collected using Remote Cortex 5.95 and by Cheetah data acquisition
474 interlinked with Remote Cortex 5.95. Neuronal data were acquired with Neuralynx
475 preamplifiers and a Neuralynx Digital Lynx amplifier. Unfiltered data were sampled with 24
476 bit at 32.7 kHz and stored to disc. Data were replayed offline, sampled with 16-bit and band-
477 pass filtered at 0.5-300 Hz and down sampled to 1 kHz for local field potential (LFP) data,
478 and filtered at 0.6-9 kHz for spike extraction. Eye position and pupil diameter was recorded
479 at 220 Hz (ViewPoint, Arrington Research). Pupil diameter was recorded for 75 (90.4 %) of
480 recordings.

481 All data analyses were performed using custom written Matlab (the Mathworks) scripts.

482

483 [Data preprocessing, trial selection and channel selection](#)

484 We corrected for any noise common to all channels via common average reference, in
485 which the average of all channels is subtracted from each individual channel. We extracted
486 population activity by progressively lowering spike extraction thresholds until approximately
487 100 Hz spiking activity was detected on each channel between fixation onset and the first
488 dimming event. Next, we computed the envelope of MUA (MUAe) by low-pass filtering
489 (<300 Hz, fifth order Butterworth) the rectified 0.6-9 kHz filtered signal. Because we noticed
490 that during some recording sessions the electrode seemed to have moved (e.g. due to
491 movement of the monkey), we visually inspected the stability of each recording by
492 investigating the stimulus aligned firing rates, MUAe and their baseline (-500 to -50 ms)
493 energy across all trials and channels. With energy (E) defined as:

$$494 \quad E = \int_i^t V(i)^2$$

495 , where t is the number of time points in the vector (V) representing the single-trial
496 histogram or MUAe. We selected the largest continuous time window that showed stable
497 activity across all V1 & V4 channels.

498 In addition to selecting trials from stable periods, we selected channels for further
499 processing that were determined to be in gray matter. Using current source density (CSD),
500 we investigated on which channels currents were entering (sinks) and exiting (sources)
501 cortical tissue, which allowed us to determine the relative recording depth compared to the
502 known cortical anatomy (Schroeder, 1998; Schroeder et al., 1991). The CSD profile can be
503 calculated according to the finite difference approximation, taking the inverse of the second
504 spatial derivative of the stimulus-evoked voltage potential φ , defined by:

$$505 \quad CSD(x) = \frac{\varphi(x+h) - 2\varphi(x) + \varphi(x-h)}{h^2}$$

506 , where x is the depth at which the CSD is calculated and h the electrode spacing (150 μm).
507 We used the iCSD toolbox (Pettersen et al., 2006) to compute the CSD. With this toolbox we
508 used a spline fitting method to interpolate φ smoothly between electrode contacts. We

509 used a diameter of cortical columns of 500 μm (Mountcastle, 1957), and tissue conductance
510 of 0.4 Sm^{-1} (Logothetis et al., 2007).

511 To aid determination of recording depth, we computed the signal-to-noise ratio (SNR), the
512 response latencies to stimulus onset for each channel and the receptive field (RF) estimation
513 (see below). SNR was computed as:

$$514 \quad SNR = \frac{\text{Signal} - \text{Noise}}{\sigma_{\text{noise}}}$$

515 , with *Signal* defined as the average MUAe amplitude in one of eight 50 ms time windows,
516 from 30 to 80 ms, in 10 ms steps, to 100 to 150 ms after stimulus onset, and *Noise* as the
517 average MUAe amplitude during the baseline period (-200 to 50 ms) before stimulus onset.
518 SNR in at least one of these eight estimates was required to be higher than 3 for a channel
519 to be included for further analyses.

520 We computed the response latency to stimulus onset for each channel according to the
521 method described by Roelfsema et al. (2007). We fitted the visual response as a
522 combination of an exponentially modified Gaussian and a cumulative Gaussian using a non-
523 linear least-squares fitting procedure (function `lsqcurvefit`) to the average MUAe time
524 course. There are two assumptions implicit in this method. First, the onset latency has a
525 Gaussian distribution across trials and across neurons that contribute to the MUAe, and
526 second, that (part of) the response dissipates exponentially. The visual response y across
527 time t was modelled as:

$$528 \quad y(t) = d \cdot \text{Exp}(\mu\alpha + 0.5\sigma^2\alpha^2 - \alpha t) \cdot G(t, u + \sigma^2\alpha, \sigma) + c \cdot G(t, \mu, \sigma)$$

529 , where μ is the mean, σ is the standard deviation, α^{-1} is the time constant of the
530 dissipation, $G(t, \mu, \sigma)$ is a cumulative Gaussian, and c and d are the factors scaling the non-
531 dissipating and dissipating modulation of the visual response. The response latency was
532 defined as the time point where $y(t)$ reached 33% of the maximum of the earliest peak, the
533 first Gaussian (Roelfsema et al., 2007; Self et al., 2013). Data were aligned to the earliest
534 current sink, the presumed thalamic input layer (L4); channels were excluded if they were
535 >1 mm more superficial or >0.75 mm deeper than this layer.

536

537 Receptive field estimation

538 Offline RFs were determined for each channel via reverse correlation of the MUAe signal to
539 stimuli (0.5 – 2 ° black squares) presented on a 9 × 12 grid (Gieselmann and Thiele, 2008).
540 The stimulus-response map was converted to z-scores, after which the RF for each channel
541 was indicated by a contour (thresholded at a z-score of 3) surrounding the peak activity.
542 These z-scored maps were averaged across all channels for each area (the population
543 average z-score was computed using Stouffer’s Z-score method according to $Z =$
544 $\sum_{i=1}^k Z_i / \sqrt{k}$, with k as the number of channels, after which we determined the overlap and
545 separation between the V1 and V4 RFs (Fig 1B-C).

546

547 Bipolar re-referencing

548 To ensure that global signals, common to multiple channels, did not affect our LFP and
549 spectral analyses (see below), we re-referenced our LFP signals according to the bipolar
550 derivation. Bipolar re-referenced LFP signals (LFPb) were computed by taking the difference
551 between two neighboring channels.

552

553 Attentional modulation

554 The effect of selective attention on neural activity was computed via an attention
555 modulation index (*attMI*), defined as:

$$556 \quad attMI = \frac{A_{RF} - A_{out}}{A_{RF} + A_{out}}$$

557 , with A_{RF} as the neural activity when attention was directed towards the RF, and A_{out} the
558 activity when attention was directed away from the RF. This index ranges from -1 to 1, with
559 zero indicating no attentional modulation and with positive (negative) values indicating
560 higher (lower) activity when attention was directed towards the RF.

561

562 Hidden Markov Model

563 To quantify On-Off dynamics in V1 and V4, we fit a Hidden Markov Model (HMM) to the
564 population activity across all laminae. We fit the HMM both to activity from each individual

565 area, following the procedures described by Engel et al. (2016), as well as to the activity
566 from both areas simultaneously.

567 Our HMM assumes that spike counts on the recorded channels can be well characterized as
568 a doubly-stochastic process, of which the parameters can be accurately estimated (Rabiner,
569 1989). In this study, spike counts on each channel are assumed to be produced by a Poisson
570 process with different (constant) mean rates during On or Off phases of the underlying
571 ‘hidden’ (latent) process s common to all channels that we need to infer (Engel et al., 2016).
572 The mean firing rate on each channel j in phase s is defined by entry λ_j^s in the emission
573 matrix Λ . The transition matrix P gives the probabilities of transitioning between these
574 latent phases. In the transition matrix P , each entry indicates the probability of transitioning
575 between two specific phases. For instance, P_{11} indicates the probability of transitioning
576 from $s = 0$ to $s = 0$ (remaining in the Off phase), whereas P_{12} indicates the probability of
577 transitioning from $s = 0$ to $s = 1$, more formally: $P_{11} = P_{off} = P(s_{t+1} = 0 | s_t = 0)$,
578 $P_{12} = 1 - P_{off} = P(s_{t+1} = 1 | s_t = 0)$. These probabilities do not depend on time: at any
579 time step t , the probability of transitioning between phases depends only on the value of s
580 at time t (s_t). The latent dynamics estimated by the HMM thus follow a discrete time series
581 in which s_t summarises all information before time t . For each channel, MUA was
582 discretized by determining spike counts in 10 ms bins following each time t , with the
583 probability of observing spike count n on channel j during phase s defined as

584
$$P(n|s) = \frac{(\lambda_j^s)^n}{n!} e^{-\lambda_j^s}$$

585 The full description of an HMM is given by the emission matrix Λ , transition matrix P and
586 the probabilities π^0 that indicate the initial values s_0 , in which $\pi_i^0 \equiv P(s_0 = i)$. These
587 parameters were estimated using the Expectation Maximization (EM) algorithm (Bishop,
588 2006), maximizing the probability of observing the data given the model according to the
589 Baum-Welch algorithm (Rabiner, 1989). Because the EM procedure can converge to a local
590 maximum, rather than the global maximum, we repeated the EM procedure ten times with
591 random parameter initializations, and chose the model with the highest likelihood. Random
592 values were drawn from Dirichlet distributions for π^0 and P , and from a uniform distribution
593 between zero and twice the channel’s mean firing rate for Λ . The EM procedure was
594 terminated if the relative change, computed as $|new - original|/|original|$, in the log-

595 likelihood was smaller than 10^{-3} and the change in the transition and emission matrix was
596 smaller than 10^{-5} , or if it reached the maximum number of iterations ($n = 500$).

597 Once the optimal parameters were estimated, we used the Viterbi algorithm to determine
598 the most likely latent trajectory for each individual trial. We applied the HMM separately to
599 each attention condition. For every trial, we applied the HMM during multiple time periods
600 of the task, during fixation and during the time window from 400 ms after cue onset to 30
601 ms after the first dimming event. For the behavioral analysis, we additionally analyzed the
602 period up to 30 ms after the second dimming event for trials in which target dimming did
603 not occur on the first dimming event, and for which the first distractor dimming was not
604 inside the RFs.

605 To determine what number of latent phases best described the data, we fit HMMs with the
606 number of phases ranging from 1 to 8, and used a four-fold cross-validation procedure to
607 compute the leave-one-channel-out cross-validation error for each HMM (Engel et al.,
608 2016). We fit the HMM to a randomly selected subset of 3/4 of the trials, and computed the
609 cross-validation error on the remaining 1/4 of trials. This procedure was repeated 4 times
610 using a different 3/4 of trials for training and 1/4 of trials for testing the HMM. We
611 computed the cross-validation error CV_{var} for each channel j across all trials K and time
612 bins T as the difference between the actual and expected spike count according to:

$$613 \quad CV_{var}[n_j] = \sum_{k=1}^K \sum_{t=1}^T (n_t^j - \lambda_j^{st})^2$$

614 We normalized CV_{var} to the error in the 1-phase HMM, averaged across channels, cross-
615 validations and conditions, and determined the difference in CV_{var} with each additional
616 phase in the HMM. The normalized mean cross-validation error across each of the eight
617 HMM models for all recordings is depicted in Fig. S1. For most recordings, and for both V1
618 and V4, CV_{var} decreased with the addition of a second phase, but did not decrease much
619 further with additional phases. This allowed the identification of the elbow (kink) in this
620 error plot as the model with two phases. We included areas/recordings for further analysis
621 that revealed a reduction in cross-validation error of at least 10% with the addition of a
622 second phase, but did not decrease by more than 10% with additional phases. For a small
623 subset of recordings, a three or a four-phase model fit the data best; these recordings were
624 excluded from further analysis. In total, we found a reduction of >10% in cross-validation

625 error when fitting a 2-phase versus 1-phase model in 64 V1 (83.1 %), and 73 V4 (92.4 %)
626 recordings; in 57 (78.1 %) recordings we found evidence for a 2-phase model in both V1 and
627 V4 (Fig. S1).

628 To investigate the across-area coordination of On-Off dynamics, we fit a 4-state HMM to V1
629 and V4 data simultaneously. Across these four states, both V1 and V4 could be in either an
630 Off or On phase, with the states defined as: $V1_{off} - V4_{off}$ (state 1), $V1_{on} - V4_{off}$ (state
631 2), $V1_{off} - V4_{on}$ (state 3) and $V1_{on} - V4_{on}$ (state 4). This model was fit according to the
632 same steps as the HMM applied to individual areas, with one exception. For each channel j ,
633 the emission rate λ was constrained to be the same across states for which this channel
634 (area) was in the same phase. For example, rates were constrained for a V1 channel across
635 state 1 and state 3, during which V1 was in an Off phase ($\lambda_j^{s=1} = \lambda_j^{s=3}$, $j \in V1$).

636

637 [Testing the effect of On-Off dynamics on behavioral performance](#)

638 To determine the effect of On-Off dynamics and their across-area coordination on
639 behavioral performance, we investigated whether the On/Off phase of population activity at
640 the time of target dimming influenced reaction times (RT). To this end, we averaged, for
641 each recording, the RT across all trials that ended in the same phase. We subsequently
642 tested for a relationship between On/Off phase and RT across recordings (Statistical
643 testing).

644

645 [Cross correlation](#)

646 The temporal relationship between On-Off time series and transitions, microsaccade onset
647 times and activity in V1, V4 and FEF were investigated using cross-correlations. The cross-
648 correlations based on HMM time series (CC_{HMM}) were calculated using the function `xcorr` in
649 Matlab, according to:

$$650 \quad CC_{HMM}(\tau) = \frac{1}{M} \sum_{m=1}^M \frac{\sum_{t=1}^T x(t)y(t+\tau)}{\sqrt{\sum_{t=1}^T |x(t)|^2 \cdot \sum_{t=1}^T |y(t)|^2}}$$

651 , where M is the number of trials, T is the number of discrete time bins, x and y the mean
652 subtracted On-Off time series in V1 and V4 as determined by the HMM, and τ the time lag.

653 Here, the numerator indicates the cross-covariance, which is normalized (the denominator)
654 such that the autocorrelation for each time series at zero lag is 1. This procedure normalized
655 CC_{HMM} such that correlation coefficients were obtained. We furthermore subtracted the
656 shuffle predictor $CC_{shuffle}$ from CC_{HMM} to remove any task-related (event-locked)
657 correlations between x and y . $CC_{shuffle}$ was computed by shuffling y trials.

658 Cross-correlations (CC) between state transitions and microsaccade onset times were
659 computed in the same way but for a different normalization (denominator) factor. Here we
660 normalized by the number of microsaccades, resulting CC to be of the order of coincidences
661 of state transitions per microsaccade.

662 To investigate the neural activity around the time of On-Off transitions, we computed the
663 transition-triggered average (TTA). The TTA was estimated by computing the cross
664 covariance (the numerator), divided by the number of transitions for each channel
665 (denominator). Again, we subtracted the shuffle predictor to remove any task-related
666 correlations.

667

668 Power estimation

669 We estimated the power spectra of the LFPb using a custom multitaper approach based on
670 the Chronux toolbox (Bokil et al., 2010). We estimated the power separately for On and Off
671 states determined by the HMM using only epochs that lasted longer than 250 ms. Because
672 epoch durations were variable, we zero-padded each segment to the next highest power of
673 2 of the longest epoch duration (2048 time points), ensuring we could extract the same
674 frequencies for each segment. This approach gave us a half bandwidth (W) of approximately
675 1.95 Hz, according to $W = (K + 1)/2T$, with K being the number of data tapers ($K = 7$) and
676 T the length of the time window in seconds. Frequencies were estimated from 4 to 200 Hz.

677

678 Microsaccade detection

679 We low-pass filtered the horizontal and vertical eye traces at 30 Hz (2nd order Butterworth
680 filter) after which we detected microsaccades by using the algorithm developed by Engbert
681 and Kliegl (2003). This algorithm converts eye position to velocity and classifies an eye
682 movement as a microsaccade if the velocity is larger than a threshold for at least three

683 consecutive time points. The threshold is set to 6 times the median estimator, given by:
684 $\sqrt{\text{median}(x^2) - \text{median}(x)^2}$, where x is the eye position channel. Thus, the threshold is
685 determined for each single trial. The use of the median estimator ensured that
686 microsaccade detection is relatively robust to different levels of noise.

687

688 Statistical testing

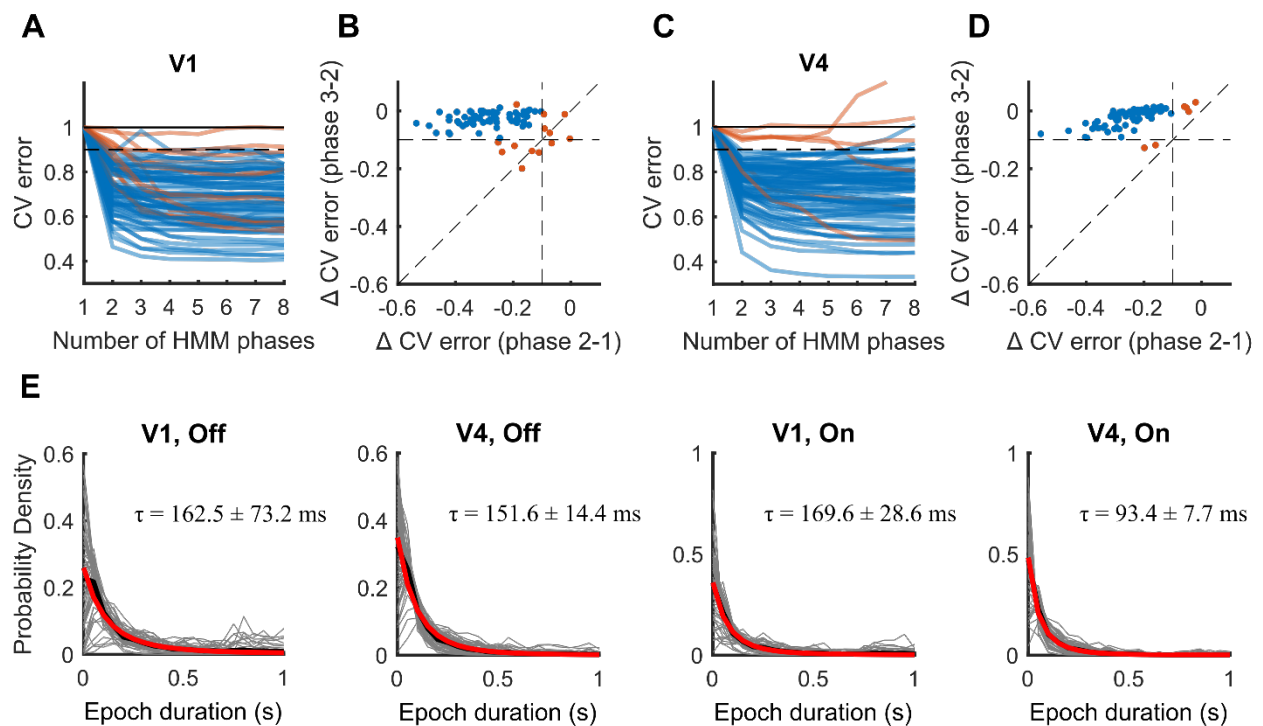
689 To determine whether there were significant differences between attention conditions or
690 HMM states (e.g. in firing rate or epoch duration) we made use of multiple statistical
691 methods. We used (paired-sample) Wilcoxon signed rank tests whenever a comparison was
692 made between two conditions (e.g. attend RF versus attend away), or to test whether a
693 distribution was significantly different from zero. When a comparison involved multiple
694 conditions, or multiple factors (e.g. attention and state), we used linear mixed effect models
695 to test for main effects of each condition/factor and interaction effects between factors.
696 These factors were defined as fixed effects and we included random intercepts for each
697 recording as random effects, accounting for the repeated measurements within each
698 recording. Specifically, we modelled RT as a linear combination of attention condition (*Att*)
699 and HMM state coefficients, as well as their interaction:

$$700 \quad RT \sim \beta_0 + \beta_1 Att + \beta_2 HMM + \beta_3 Att \cdot HMM$$

701 We used false discovery rate (FDR) to correct for multiple comparisons (Benjamini and
702 Yekutieli, 2001). Error bars in all figures indicate the standard error of the mean (SEM).

703

704



705

706 **Fig. S1. Determining the number of HMM phases and their epoch durations in V1 and**

707 **V4 MUA. (A)** Cross validation (CV) error plotted against the number of phases in each

708 HMM for V1. **(B)** The difference in cross validation error between the 1-phase and 2-phase

709 model, plotted against the difference between the 2-phase and 3-phase model for V1. Most

710 recordings show a large reduction in cross-validation error with the addition of a second

711 phase, and only marginal changes with additional phases. Blue (red) lines and markers

712 indicate the recordings included (excluded) for further analysis. **(C-D)** Same conventions as

713 **(A-B)** but for V4. **(E)** Distributions of Off and On episode durations overlaid by the

714 exponential distributions with the decay constant set by the HMM transition probabilities

715 (red, $N(t) = N_0 e^{-t/\tau}$, where N_0 is the normalization constant, and τ is the decay time-

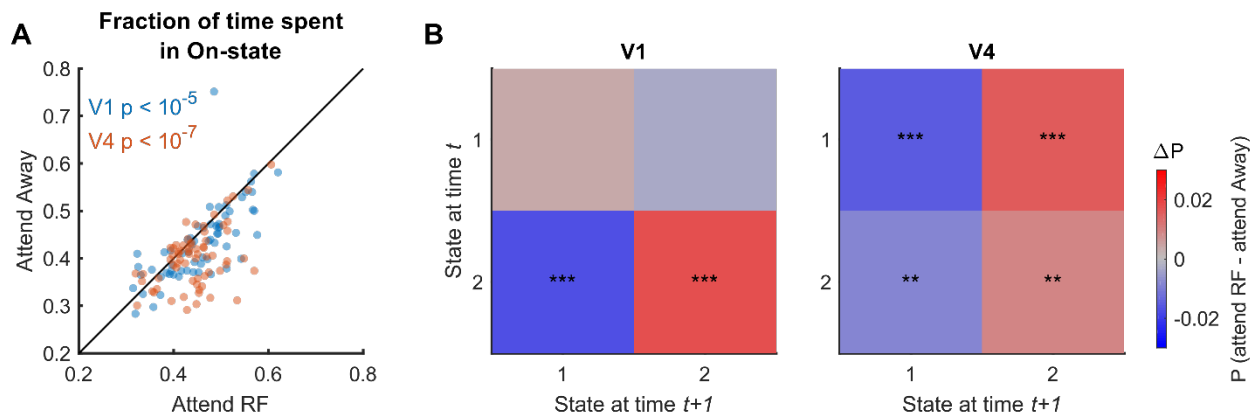
716 constant computed for each recording and phase). A good match for these models indicates

717 that On-Off dynamics were not driven by an oscillatory phenomenon. Grey and thick black

718 lines indicate individual recordings and their mean, respectively.

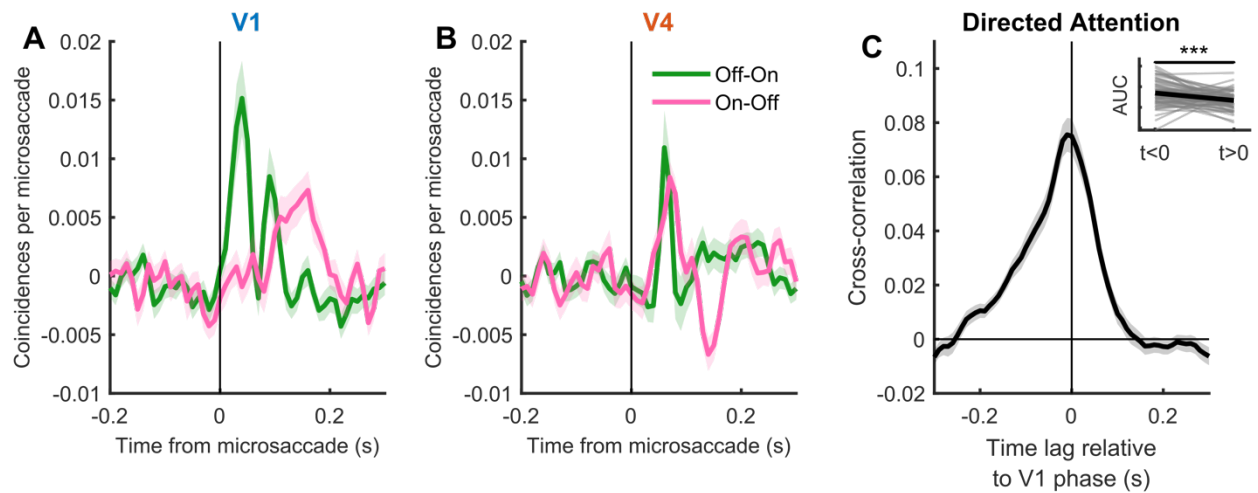
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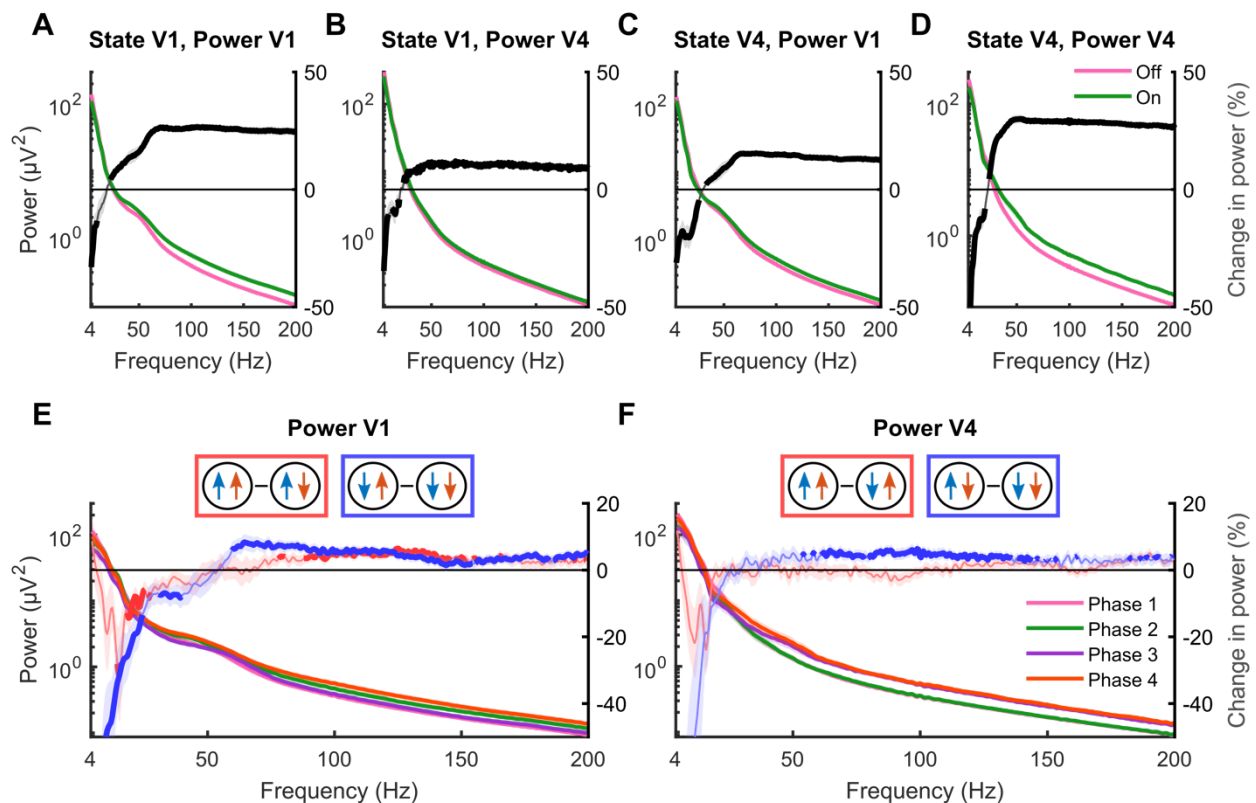
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722 **Fig. S2. Attentional modulation of HMM parameters.** (A) The fraction of time spent in an
723 On phase is increased when attention is directed towards the RFs. (B) Attentional influence
724 on HMM transition probabilities. Shown is the difference between transition matrices (attend
725 RF – attend Away). Statistics: Wilcoxon signed rank tests; *, **, ***, indicate FDR corrected
726 significance levels of $p < 0.05$, $p < 0.01$ and $p < 0.001$, respectively.



727

728 **Fig. S3. Relationship between microsaccades and On-Off transitions.** (A) Cross-
729 correlation of On-Off transitions in V1 triggered to microsaccade onset. (B) Same as panel A,
730 but for On-Off transitions in V4. (C) Cross-correlation between time series of On-Off
731 dynamics in V1 and V4 after exclusion of trials in which microsaccades occurred. Statistics:
732 Wilcoxon signed rank test. Shaded regions denote ± 1 SEM across recordings, *, ** and ***
733 indicate significance levels of $p < 0.05$, $p < 0.01$ and $p < 0.001$ respectively.

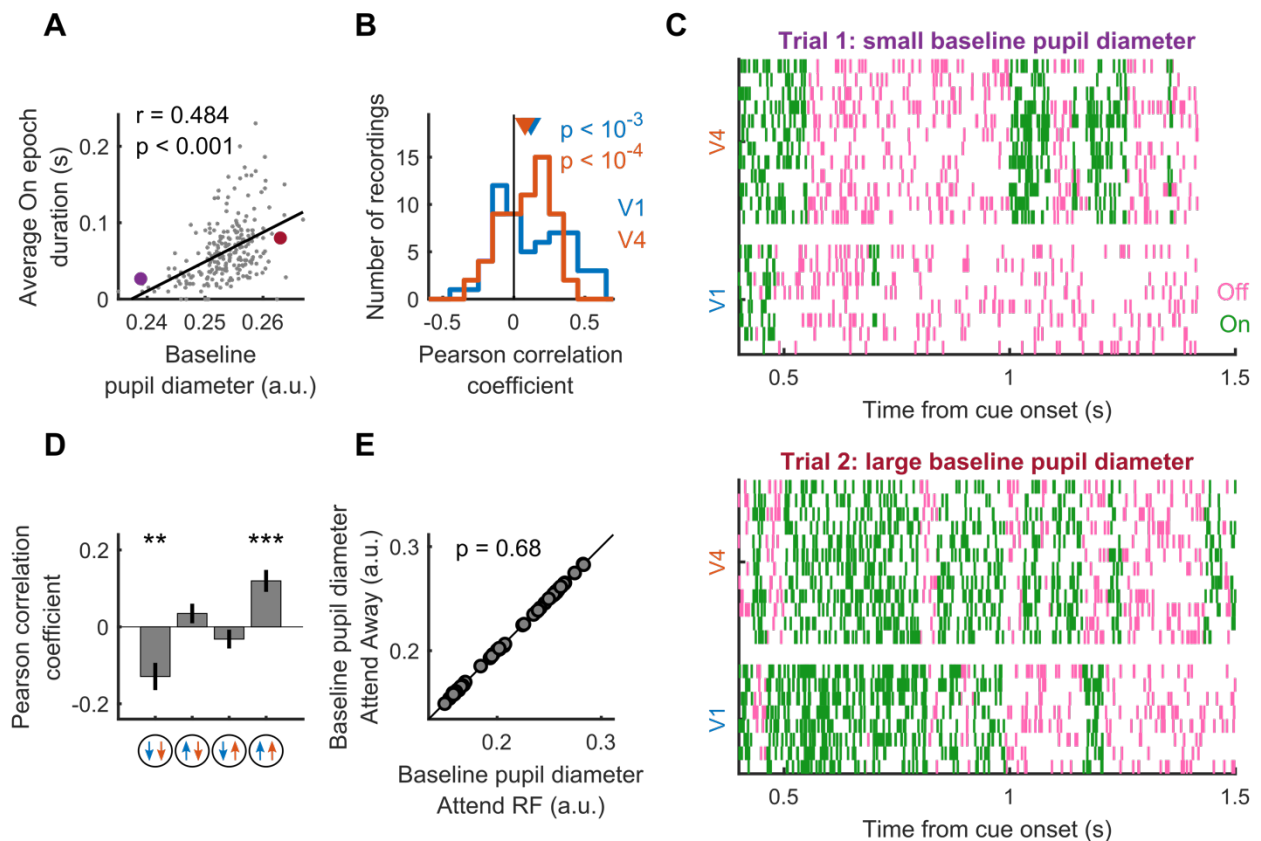


734

735 **Fig. S4. Bipolar re-referenced LFP power spectrum across HMM states.** (A) Power in
 736 V1 during On and Off phases in V1. (B) Power in V4 during On and Off phases in V1. (C)
 737 Power in V1 during On and Off phases in V4. (D) Power in V4 during On and Off phases in
 738 V4. Right y-axis indicates the percentage change in power during On versus Off phases (On-
 739 Off). (E-F) Power spectrum in V1 (E) and V4 (F) for the 4-state HMM fit across V1 and V4
 740 and the within-area power difference between On phases (red, V1: state 4-2; V4: state 4-3),
 741 or Off phases (blue, V1: state 3-1; V4: state 2-1). Only On/Off episodes of at least 250 ms
 742 were included. Thick percentage change lines indicate significantly modulated frequencies (p
 743 < 0.05 , Wilcoxon signed rank test, FDR corrected). Shaded regions denote ± 1 SEM.

744

745



746

747 **Fig. S5. The relationship between baseline pupil diameter and On/Off episode**

748 **durations.** (A) Example recording showing that baseline pupil diameter is positively

749 correlated to the average On episode duration in V1. Each dot represents one single trial, r is

750 the Pearson correlation coefficient. The purple and red dot indicate the example trials used in

751 panel C. (B) Across recordings, the average duration of On epochs in both V1 and V4 is

752 positively correlated with the size of the baseline pupil diameter. (C) Two example trials in

753 which the average On epoch duration is larger on the trial with larger (bottom) compared to

754 the trial with smaller (top) baseline pupil diameter. (D) Across recordings, baseline pupil

755 diameter is negatively (positively) correlated with the average epoch duration when both V1

756 and V4 are in an Off (On) phase. (E) The average baseline pupil diameter during attend RF

757 conditions plotted against attend away conditions. There is no difference between attention

758 conditions. Each dot represents a recording session. Statistics: Wilcoxon signed rank test

759 (FDR corrected) (B, D, E) and Pearson correlation (A). Error bars and shaded regions denote

760 ± 1 SEM, and *, ** and *** indicate significance levels of $p < 0.05$, $p < 0.01$ and $p < 0.001$

761 respectively.

762

763

764

	Red	Green	Blue
Monkey 2 & 3, and monkey 1 (n=4)	a. [220 0 0] – 12.8 b. [140 0 0] – 4.2	a. [0 135 0] – 12.9 b. [0 90 0] – 4.6	a. [60 60 255] – 12.2 b. [30 30 180] – 4.6
Monkey 1 (n=1)	b. [170 0 0] – 6.7	b. [0 105 0] – 6.4	b. [37 37 210] – 6.6
Monkey 1 (n=1)	b. [175 0 0] – 7.2	b. [0 105 0] – 6.4	b. [40 40 220] – 7.7
Monkey 1 (n=8)	b. [180 0 0] – 7.7	b. [0 110 0] – 7.3	b. [40 40 220] – 7.7

765 **Table S1.**

766 Color values used for the 3 colored gratings across recording sessions and subjects, indicated
767 as [RGB] – luminance (cd/m²). a = Undimmed values, b = Dimmed values. For monkey 1,
768 we used a variety of dimmed values across recordings.

769