Pairwise correlations of spiking activity changes along the ventral visual cortical pathway of macaque monkeys

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Abbreviated title: Correlations of spiking activity in IT, V4, and V1

Number of pages: 35; *Number of Figures:* 5; *Number of Tables:* 0

Word counts: *Abstract,* 237; *Introduction,* 630; *Discussion,* 1342

Acknowledgements: I thank H. Kaneko for technical assistance and R. Takeuchi for valuable comments on an earlier version of the manuscript. Monkeys were provided by the National BioResource Project of MEXT, Japan. This work was supported by Grant-in-Aid for Scientific Research on Innovative Areas: “Innovative SHITSUKAN Science and Technology (No. JP15H05921) and “Non-linear Neuro-oscillology” (No. JP16H01612) from MEXT, Japan. We thank Adam Phillips, PhD, from Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript. The authors declare no competing financial interests.

22 **Abstract**

23 Spiking activity often correlates across neurons in the cerebral cortex. Precise spike-timing
 24 correlation at millisecond scale reflects underlying neural circuitries. Correlations of stimulus
 25 evoked spiking activities affects the distributions of spike counts in a multi-neuron space and
 26 reflects stimulus encoding ability of neuron populations. The present study compared the degree
 27 of spiking-activity correlation among three areas of the macaque visual system to determine
 28 whether neural circuitry and the way to encode stimulus-related information by neuron
 29 populations are unique to each area. Spiking activity of multiple single neurons was recorded in
 30 macaque primary visual cortex (V1), visual association cortex (V4), and inferior temporal
 31 cortex (IT). Cross-correlation of spike trains revealed that single-neuron pairs in IT exhibited
 32 the highest incidence of precisely correlated firing, whereas V1 pairs showed the lowest
 33 incidence. Although noise correlation, which quantifies similarity in trial-to-trial response
 34 fluctuations, differed among cortical areas, signal correlation, which quantifies similarity in
 35 stimulus preferences, did not. The degree of temporally precise correlation was positively
 36 related to the signal-correlation strength in all three cortical areas and the relation of IT pairs
 37 was stronger than that of V1 pairs. Temporally precise correlations between single-neuron and
 38 population-level activity also differed among cortical areas and V1 neurons exhibited the lowest
 39 incidence of correlated firing with population activities. The differences in spiking-activity
 40 correlations among visual cortical areas suggest that each cortical area has unique neuronal
 41 circuitry for representing information, and which performs unique neuronal computations.

42

43 **Significance Statement**

44 Although hierarchical information processing plays a crucial role in the brain and in artificial
45 neural networks, whether hierarchically connected brain areas share neural circuitry and
46 information representation remains unclear. Here, we examined spiking activity across the
47 ventral visual system in macaque monkeys and found that cortical areas differed in how
48 correlated their spiking activity was, suggesting that neural circuitry and the way to encode
49 stimulus-related information by neuron populations are unique to each cortical area.

50

51 **Introduction**

52 Spiking activity in the cerebral cortex correlates across individual neurons. Precise
53 spiking-activity correlation at the millisecond scale reflects the organization of underlying
54 neural circuitry (Perkel et al., 1967; Moore et al., 1970; Bryant et al., 1973). For example,
55 correlated activity without time delay reflects common inputs to paired neurons. Precise
56 spiking-activity correlation have been proposed to encode stimulus related information (Singer
57 and Gray, 1995; Diesmann et al., 1999; Hirabayashi and Miyashita, 2005; Panzeri et al., 2015;
58 Zandvakili and Kohn, 2015). Thus, studying correlations at the millisecond scale allows us to
59 infer neural circuitry between paired neurons and information encoding by synchrony. Two
60 other types of spike correlation related to amount of information encoded by neuron populations
61 (Averbeck et al. 2006; Cohen and Kohn, 2011; Panzeri et al., 2015; Franke et al., 2016). Signal
62 correlation refers to the correlation between trial-averaged spike counts of paired neurons,
63 which reflects the similarity in stimulus-evoked responses (Gawne and Richmond, 1993;
64 Panzeri et al., 2015). If neurons in a population encode independent information, signal
65 correlation is low, whereas if they encode redundant information, signal correlation is high.
66 Responses of cortical neurons varies from one trial to another. Noise correlation—or spike
67 count correlation—refers to the correlation between the deviations of single-trial spike counts
68 from the trial-averaged response of paired neurons, and reflects the similarity of trial-to-trial
69 response fluctuations (Zohary et al., 1994). Relationship between degrees of noise correlation
70 and information encoding ability of a neuron population may not be straightforward. Correlated
71 noise may limit or enhance the ability of a neuron population to encode information depending
72 on the sign of signal correlation (Zohary et al., 1994; Cohen and Kohn, 2011; Panzeri et al.,

73 2015).

74 Such correlations in spiking activity have been examined extensively, especially in
75 the visual cortical areas of primates (Krüger and Aiple, 1988; Ts'o and Gilbert, 1988; Gochin et
76 al., 1991; Kreiter and Singer, 1992; Gawne and Richmond, 1993; Zohary et al., 1994; Gawne et
77 al., 1996; Tamura et al., 1996; Roe and Ts'o, 1999; Maldonado et al., 2000; Bair et al., 2001;
78 Tamura et al., 2004; Aggelopoulos et al., 2005; Hirabayashi and Miyashita, 2005; Kohn and
79 Smith, 2005; Tamura et al., 2005; Kreiman et al., 2006; Smith and Kohn, 2008; Cohen and
80 Maunsell, 2009; Kotake et al., 2009; Mitchell et al., 2009; Sato et al., 2009; Ecker et al., 2010;
81 Huang and Lisberger, 2013; Smith and Sommer, 2013; Ecker et al., 2014; Goris et al., 2014; Lin
82 et al., 2014; Tamura et al., 2014; Hung et al., 2015; Okun et al., 2015; see Cohen and Kohn,
83 2011, for a review of noise correlation). If neural circuitry and information encoding are shared
84 among cortical areas, the degree to which spiking activity is correlated might be similar across
85 cortical areas. Conversely, if the circuitry and information encoding are unique to each cortical
86 area, spiking-activity correlation might differ among them. Although a few studies have directly
87 compared correlations in spiking activity between two visual cortical areas (Gawne et al., 1996;
88 Tamura et al., 1996; Smith and Sommer, 2013), whether spike-correlation systematically differs
89 along hierarchically connected cortical regions remains unclear.

90 The present study aimed to clarify whether a variety of correlations between the
91 spiking activity of paired neurons differ among the primary- (V1), middle- (V4), and late-stage
92 (inferior temporal cortex, IT) visual cortical areas of macaque monkeys. Because these areas
93 comprise the hierarchically organized ventral visual cortical pathway, they are ideal for
94 assessing whether correlations change systematically along the cortical hierarchy. Correlations

between the spiking activities of paired neurons in each cortical area revealed that some types of correlations differed among the three regions and changed systematically along the visual cortical hierarchy. Relationships between the spiking activity of single neurons and that of adjacent neurons as a population also differed among the three cortical areas.

Materials and Methods

The general experimental procedures have been described previously (Tamura et al., 2016), and the present study analyzes the data obtained in the previous study. Briefly, neuronal activity was recorded from three monkeys (*Macaca fuscata*; body weight, 5.9–8.6 kg; Monkeys A, B, C). Recordings from IT cortex were obtained from all three monkeys and those from V4 and V1 were obtained from two monkeys (Monkeys A and C). The monkeys were anesthetized and paralyzed because body movements affect recording stability and eye movements affect the response variance and correlation of neuronal spiking activity (Gur et al., 1997; Maldonado et al., 2008; McFarland et al., 2016). Because anesthesia has been shown to increase noise correlation (Ecker et al., 2014), the correlation measures should be interpreted with caution (but see Discussion). All experiments were performed in accordance with the guidelines from the National Institute of Health (1996) and the Japan Neuroscience Society, and were approved by the Osaka University Animal Experiment Committee.

Initial preparatory surgery

To prepare the monkeys for the recordings, a head restraint was implanted and the lateral or occipital part of the skull (over the recording region) was covered with acrylic resin. Monkeys

117 were fully anesthetized during surgery by inhalation of 1%–3% isoflurane (Forane, Abbott
118 Japan, Tokyo, Japan) in nitrous oxide (70% N₂O, 30% O₂) through an intratracheal cannula.
119 Antibiotics (Pentacilin, Toyama Chemical, Tokyo, Japan; 40 mg/kg, i.m.) and an
120 anti-inflammatory and analgesic agent (Voltaren, Novartis, Tokyo, Japan; or Ketoprofen, Nissin
121 Pharmaceutical, Yamagata, Japan) were administered immediately after the surgery and during
122 the first postoperative week. After 1–2 weeks of recovery, the monkeys' eyes were examined to
123 select appropriate contact lenses that would focus images placed 57 cm from the cornea on the
124 retina. The retinal fundus was photographed to determine the position of the fovea.

125

126 ***Preparation of animals for neural recording***

127 On the day of neural recording, monkeys were sedated via intramuscular injection of atropine
128 sulfate (0.1 mg/kg) and ketamine hydrochloride (12 mg/kg). The monkeys were then
129 anesthetized by inhalation of 1%–3% isoflurane in nitrous oxide (70% N₂O, 30% O₂) through
130 an intratracheal cannula and by an infusion of the opioid fentanyl citrate (Fentanest, Daiichi
131 Sankyo; 0.035 mg/kg/h) in lactated Ringer's solution. A small hole (~7 mm) was drilled in the
132 resin-covered skull and a small slit (2 mm) was made in the dura to insert electrodes. The pupil
133 was dilated and the lens was relaxed using 0.5% tropicamide/0.5% phenylephrine hydrochloride
134 (Mydrin-P, Santen, Osaka, Japan). The cornea was then covered with the contact lens that
135 included an artificial pupil (3 mm diameter). After inserting the recording electrode, vecuronium
136 bromide (Masculax, MSD, Tokyo, Japan; 0.06 mg/kg/h) was added to the infusion solution to
137 prevent eye movements while recording neuronal activity. After each recording session,
138 monkeys were given analgesics and antibiotics and returned to their home cages. Each

139 recording session lasted up to 7 h, and consecutive recording sessions in the same monkey were
140 separated by at least one week.

141

142 ***Neuronal-activity recordings***

143 Spiking activity from multiple-single neurons was recorded in IT, V4, and V1 using a
144 single-shaft electrode with 32 recording probes arranged linearly (A1X32-10 mm 50-413;
145 NeuroNexus, Ann Arbor, MI, USA). The distance between the centers of adjacent recording
146 probes was 50 μ m. Because spiking activity from the same neuron could be picked up by two or
147 more adjacent probes, single neuron activity was isolated offline using custom-made software
148 (see Kaneko et al. 1999; Kaneko et al. 2007; Tamura et al. 2014, for details). Spikes were
149 classified with reference to the signals recorded from five consecutive probes (*i.e.*, within 0.2
150 mm). Care was taken not to assign single spikes to two or more neurons. A neuron's position
151 along the electrode was defined as the position of the probe that recorded its spikes at the largest
152 amplitude.

153 Recordings were made in 10 recording sessions for the IT, and 8 sessions each for V4
154 and V1. The recording sites in IT were located between the superior temporal sulcus and the
155 anterior middle temporal sulcus, and anterior to the posterior middle temporal sulcus. Those in
156 V4 were located between the superior temporal sulcus and the lunate sulcus, and those in V1
157 were located on the surface of the occipital cortex away from the lunate sulcus.

158

159 ***Visual stimuli***

160 The stimulus set comprised 64 color images (8 each from 8 categories of natural objects: stones,

161 trees bark, leaves, flowers, fruits and vegetables, butterfly wings, feathers, and skin and fur) and
 162 a blank image with the same pixel values as the background (Tamura et al., 2016). All images
 163 were 6° in visual angle. Images were presented on a liquid crystal display (CG275W, Eizo,
 164 Ishikawa, Japan), which was regularly calibrated with the internal calibrator and checked with a
 165 spectrometer (Minolta CS-1000, Tokyo, Japan). The luminance values of the white and black
 166 areas of the display were 125 cd/m² and 1.3 cd/m², respectively. Each image was presented for
 167 200 ms with the inter-stimulus interval of 200 ms. Stimulus onsets and offsets were recorded
 168 using a photodiode attached to the monitor. Each stimulus image was presented 25 times during
 169 recording. Images were presented to the eye contralateral to the recording hemisphere, while the
 170 other eye remained closed. For IT neurons, images were presented to the fovea because the
 171 receptive fields (RFs) of IT neurons include the fovea and respond well to stimuli located there
 172 (Gross et al., 1972). For V4 and V1 neurons, images were presented to the center of the RF, as
 173 determined by listening to the amplified multiunit activity while visually stimulating the
 174 neurons with hand-held circular disks, bars, or grating patterns.

175

176 ***Data analysis***

177 The magnitude of visually evoked responses were calculated for each stimulus by subtracting
 178 the spontaneous firing rate during the 100-ms period immediately preceding stimulus onset
 179 from the raw firing rate during the 200-ms stimulus presentation. The window for the 200-ms
 180 stimulus-presentation period was shifted to 80 ms after stimulus onset for IT neurons to
 181 compensate for response latency. The responsiveness of each neuron was evaluated by
 182 comparing the firing rates during the stimulus presentation period across stimuli ($P < 0.01$,

183 Kruskal–Wallis test).

184 Correlations between paired neurons were measured in three ways. Precise
185 spiking-activity correlations at millisecond-scale were calculated by cross-correlating paired
186 spike trains at a temporal resolution of 1 ms and constructing cross-correlograms (CCGs). Raw
187 CCGs were constructed using all spikes collected from the paired neurons during the entire
188 recording, including both visual-stimulation and inter-stimulus periods. The spike count in each
189 CCG bin was normalized with respect to the geometric mean of the spike counts of paired
190 neurons. Because visual stimulation activated the two neurons of a pair almost simultaneously, a
191 raw CCG reflects both the correlation due to the stimulus-locked activation (stimulus
192 coordination) and that due to functional connections between the two neurons (neuronal
193 correlation). To separate these contributions, a shift-predicted CCG was calculated by shifting
194 the timing of the spike trains from one of the two neurons by one trial (Perkel et al. 1967;
195 Toyama et al. 1981; see Tamura et al., 2014 for details). The center peaks of the CCGs were
196 detected by comparing the spike counts in each 1-ms bin of a raw CCG with those from the
197 corresponding shift-predicted CCG bin ($P < 0.0001$, binomial test). The comparison was
198 performed within a time window of ± 10.5 ms to detect significant peaks at or around the 0-ms
199 bin (center peaks). The shift-predicted CCG was subtracted from the raw CCG to obtain the
200 shift-corrected CCG. The height and width of the center peaks of shift-corrected CCGs were
201 then quantified. The heights were log transformed when performing statistical analyses.
202 Because spikes were sorted using the signals recorded from five consecutive probes and because
203 the method cannot separate spikes that occur within 0.2 ms, the spike counts in the 0-ms bin ($\pm$
204 0.5 ms) of the raw CCG for paired neurons recorded from the same or nearby probes (< 5

205 probes, 0.2 mm) might be underestimated. In other words, those separated by more than five
206 consecutive probes were not affected by this problem.

207 Signal correlation quantifies the similarity between the trial-averaged responses
208 (signal) of a pair of neurons to the 64 stimuli. Signal correlation was assessed using the Pearson
209 correlation coefficient between the two sets of trial-averaged responses. Noise correlation
210 quantifies the similarities in single-trial response deviations (noise) from the signal between
211 paired neurons. The noise for each stimulus was calculated by subtracting the signal from
212 single-trial responses, then dividing the result by the standard deviation across trials (Zohary et
213 al., 1994). Noise correlation was assessed using the Pearson correlation coefficient between the
214 two sets of single-trial response deviations. Signal correlations and noise correlations were
215 Fisher transformed when performing statistical tests. Visually responsive neurons ($P < 0.01$,
216 Kruskal–Wallis test) were selected for the signal correlation and noise correlation analyses.

217 To analyze the activity of neuronal populations, population spike trains were
218 constructed by summing the spike trains from all other simultaneously recorded neurons with
219 1-ms bins (see Fig. 4A). If two or more neurons emit spikes in a 1-ms bin, the bin takes a value
220 larger than one; for example, if three neurons fire in a bin, the value of the bin is three. To
221 quantify correlation between the activity of single neurons and that of neuronal populations at
222 the millisecond scale, spike trains of single neurons were cross-correlated with population spike
223 trains at a temporal resolution of 1 ms. The resultant CCGs are termed population-neuron CCGs
224 (Okun et al., 2015, refer to them as spike-triggered population rates). Population-neuron signal
225 correlation was calculated using the Pearson correlation coefficient between the trial-averaged
226 responses of a single neuron and those of the summed responses of all other simultaneously

227 recorded neurons. Population-neuron noise correlation was assessed using the Pearson
228 correlation coefficient between a single-trial response deviation of a single neuron and that of
229 the summed responses of all other simultaneously recorded neurons.

230

231 *Experimental design and statistical analysis*

232 For statistical analyses, all the data were pooled. The details of number of neurons and neuron
233 pairs were listed in the Results section. Statistical threshold (P value) was set at 0.01, except for
234 CCG-peak detection, where it was set at 0.0001. Effect sizes for non-parametric data (r) were
235 calculated with the formula

$$236 \quad r = Z/\sqrt{N},$$

237 where Z and N represent the z-transformed Mann-Whitney U-test statistic and the number of
238 samples, respectively. Effect sizes for chi-square tests (Cramer's V) were calculated with the
239 formula

$$240 \quad \text{Cramer's } V = \sqrt{\chi^2/N \times (M - 1)},$$

241 where χ^2 is the chi-square statistic, N is the number of samples, and M is the smaller of the two
242 values among the number of the rows and columns of the contingency table. The threshold for
243 the effect size was set at 0.1. Thus, differences among populations were regarded as significant
244 if the P value was less than 0.01 and the effect size was larger than 0.1 (Cohen, 1988).

245 Statistical testing was performed using MATLAB (The MathWorks, MA) and provided exact
246 p-values except for the test for the similarity of two independent correlation coefficients that
247 was performed using a statistical software R (<https://www.r-project.org>) with the 'psych'
248 package, which does not return the exact p-values if p-values are smaller than 0.01.

249

250 **Results**

251 Neuronal activity was recorded from 189, 149, and 171 neurons from IT, V4, and V1,
252 respectively. From these neurons, 2,082 IT neuron pairs, 1,797 V4 pairs and 2,261 V1 pairs
253 were constructed. Note that single neurons contributed to multiple pairs if they were recorded
254 simultaneously.

255

256 *Comparisons of cross-correlated spiking activity among IT, V4, and V1 neuron pairs*

257 Correlations between the spiking activities of single-neuron pairs at the millisecond scale were
258 compared among IT, V4, and V1. The cross-correlation analyses of the spike trains from paired
259 neurons provided CCGs at a temporal resolution of 1 ms. The presence/absence of CCG center
260 peaks was judged statistically by comparing the spike counts in each 1-ms bin of raw CCGs
261 with those of shift-predicted CCGs within ± 10.5 ms ($P < 0.0001$, binomial test). The center
262 peak incidence for the CCGs was 14% for IT pairs (298/2,082), 10% for V4 pairs (186/1,797),
263 and 5% for V1 pairs (103/2,261; Fig. 1A). These incidences differed across the three regions (P
264 $= 2.2 \times 10^{-16}$, effect size = 0.14, chi-square test). Thus, each cortical area had a unique degree of
265 spiking-activity correlation at the millisecond scale, and the incidence of correlated neuron pairs
266 changed systematically along the cortical hierarchy.

267 Width of CCG peaks also differed systematically along the cortical hierarchy. Visual
268 inspection showed broad peaks in the CCGs of IT pairs and sharp peaks in those of V1 pairs
269 (Fig. 1B-D). The peak width of the average shift-corrected CCGs across neuron pairs with
270 significant center peaks (298 IT pairs, 186 V4 pairs, and 103 V1 pairs) can quantify this

271 impression by fitting the exponential function,

272 $y = A \times \exp(-x/\tau) + B$,

273 where y and x are the normalized spike count and CCG time delay, respectively; A is amplitude

274 and B is offset; and τ is a time constant that corresponds to the time delay until the amplitude

275 decreases to 37% of the peak. The time constant (τ) was used as a measure of the peak width,

276 and was 40.1 ms for IT pairs ($R^2 = 0.95$), 21.6 ms for V4 pairs ($R^2 = 0.85$), and 13.4 ms for V1

277 pairs ($R^2 = 0.60$). Thus, as the initial impression indicated, peak width was relatively broad for

278 IT pairs and sharp for V1 pairs. Although fitting an exponential function to the average CCGs

279 was successful, doing so for individual pairs was only successful for a small number of pairs.

280 Therefore, a *width index* (which Tamura et al., 2014, refers to as the peak-to-area ratio) was

281 used as another measure of CCG width.

282 *Width index = area under the curve/peak height*,

283 where the *area under the curve* is the sum of the spike counts under the shift-corrected CCGs,

284 and *peak height* is the spike count at the CCG center peaks. Pairs with a negative area under the

285 curve (18 IT pairs, 20 V4 pairs, 17 V1 pairs) were excluded from this analysis. The value of the

286 index ranged from 1 for neuron pairs that showed the sharpest peak (one bin width) up to 500

287 (the number of bins in CCGs) for neuron pairs that showed much broader peaks. IT pairs had

288 the largest width index with a median of 30.9 (280 pairs), followed by V4 pairs with a median

289 of 18.7 (166 pairs), and V1 pairs with the smallest median of 7.9 (86 pairs; Fig. 1E). The width

290 index differed among the three cortical areas ($P = 3.0 \times 10^{-21}$, Kruskal–Wallis test; effect size,

291 0.24 for IT-V4, 0.48 for IT-V1, 0.35 for V4-V1). These results suggest that the hierarchical

292 order in the ventral visual pathway is reflected in the temporal properties of spike interactions.

IT pairs exhibited a higher incidence of CCG peaks and broader peak width than V1 pairs. The higher incidence of CCG peaks among IT pairs was likely due to the higher incidence of CCGs with broad peaks. To examine this possibility, the incidences of CCGs with sharp peaks and broad peaks were examined separately among cortical areas. Sharp/broad peaks were arbitrarily defined as peaks with a width index smaller/larger than the median of the V1 pairs (width index, 7.9). The incidence of CCGs with sharp peaks was low and did not differ among the IT (1.6%, 34/2,082), V4 (2.1%, 38/1,797), and V1 (1.9%, 43/2,261; $P = 0.540$, effect size = 0.01, chi-square test), whereas that with broad-peaks did (IT: 11.8%, 246/2,082; V4: 7.1%, 128/1,797; V1: 1.9%, 43/2,261; $P = 2.3 \times 10^{-37}$, effect size = 0.17, chi-square test). These results suggest that the higher incidence of CCG peaks in IT pairs is likely to derive from higher incidences of CCGs with broader peaks.

304

305 ******* Figure 1 near here *******

306

307 *Comparisons of signal and noise correlations among IT, V4, and V1 neuron pairs*

308 Signal and noise correlations across the three brain regions were used to examine the
309 correlations between spiking activities over a longer timescale. Signal correlation is the
310 correlation of trial-averaged responses (signal) during the stimulus presentation period (200 ms),
311 and noise correlation is the correlation of the single-trial response deviation (noise) from the
312 signal. Visually responsive neurons ($P < 0.01$, Kruskal–Wallis test; 141 IT neurons, 86 V4
313 neurons, and 107 V1 neurons) were used for the analysis, yielding 1,291 IT pairs, 759 V4 pairs,
314 and 1,014 V1 pairs.

315 The median signal correlation was positive in all the three cortical areas (IT, 0.070;
316 V4, 0.039; V1, 0.083; Fig. 2A, B). The median signal correlation across IT pairs was different
317 from zero ($P = 1.1 \times 10^{-39}$, effect size = 0.37, Wilcoxon signed-rank test; Fig. 2A) and the signal
318 correlation of IT pairs was different from that between IT neurons recorded from different sites
319 (median = 0.018, $P = 4.1 \times 10^{-28}$, effect size = 0.11, Mann-Whitney U-test). In both V4 and V1,
320 the median signal correlation was different from zero (V4, $P = 2.2 \times 10^{-12}$, effect size = 0.25; V1,
321 $P = 6.7 \times 10^{-32}$, effect size = 0.37; Fig. 2B), but their signal correlation was not different from the
322 signal correlation between neurons recorded from different sites (V4, median = 0.026, $P =$
323 2.6×10^{-4} , effect size = 0.06; V1, median = 0.065, $P = 6.5 \times 10^{-4}$, effect size = 0.05). The signal
324 correlations did not differ among IT, V4, and V1 ($P = 0.0014$, Kruskal–Wallis test; effect size,
325 0.06 for IT-V4, 0.02 for IT-V1, 0.08 for V4-V1).

326 The median noise correlations were also positive (IT, 0.020; V4, 0.015; V1, 0.007;
327 Fig. 2C, D), and was different from zero (IT, $P = 1.4 \times 10^{-62}$, effect size = 0.46; V4, $P =$
328 3.7×10^{-23} , effect size = 0.36; V1, $P = 1.1 \times 10^{-11}$, effect size = 0.21, Wilcoxon signed-rank test) in
329 all three cortical areas. Consistent with the differences in the incidences of CCG peaks among
330 cortical areas, the noise correlations differed between IT and V1 ($P = 2.1 \times 10^{-16}$, Kruskal–Wallis
331 test; effect size, 0.09 for IT-V4, 0.17 for IT-V1, 0.09 for V4-V1), and IT pairs had the highest
332 noise correlation and V1 pairs had the lowest noise correlation.

333

334 ***** Figure 2 near here *****

335

336 *Relationship between CCG-peak height and signal correlation or noise correlation*

337 Analysis revealed that CCG-peak height correlated positively with signal correlation
 338 in all three cortical areas, (IT, $r = 0.48$, $P = 8.7 \times 10^{-74}$; V4, $r = 0.42$, $P = 1.8 \times 10^{-33}$; V1 $r = 0.28$,
 339 $P = 3.6 \times 10^{-19}$; test for independence; Fig. 3A-C), meaning that if two neurons received common
 340 inputs, they tended to share stimulus preferences. However, the degree of correlation differed
 341 depending on the region. V1 pairs exhibited lower correlation than pairs in other areas (V1-IT, P
 342 < 0.01 ; V1-V4, $P < 0.01$; V4-IT, $P = 0.12$, test for the similarity of two independent correlation
 343 coefficients; Fig. 3D), meaning that the relationship between the organization of common inputs
 344 and the similarity in stimulus preferences are less clear in V1. These results can explain the
 345 finding that signal correlation did not differ among cortical areas, despite the differences in the
 346 incidences of CCG peaks among cortical areas.

347 Similar to signal correlation, CCG-peak height correlated positively with noise
 348 correlation in all three cortical areas (IT, $r = 0.69$, $P = 1.4 \times 10^{-183}$; V4, $r = 0.51$, $P = 3.4 \times 10^{-51}$;
 349 V1 $r = 0.40$, $P = 7.5 \times 10^{-41}$; test for independence; Fig. 3E-G). Again, the degree of correlation
 350 depended on the cortical areas. IT neurons exhibited higher positive correlation than pairs in
 351 other areas, and like with signal correlation, V1 neurons displayed lower positive correlation
 352 than pairs in other areas (IT-V4, $P < 0.01$; IT-V1, $P < 0.01$; V4-V1, $P = 0.01$; Fig. 3H). These
 353 results show that the relationship between the organization of common inputs and the similarity
 354 in trial-to-trial response fluctuations differed among cortical areas.

355

356 ***** Figure 3 near here *****

357

358 *Relationships between single-neuron and population-neuron activities*

359 Although significant correlations between the spiking-activities of paired single
360 neurons were observed in all three cortical areas, they were generally weak; *i.e.*, low incidences
361 of CCG center peaks and positive but near-zero signal and noise correlations. Such weak
362 single-neuron correlations suggest that most neurons emit spikes independently from adjacent
363 neurons. However, weak single-neuron correlations may lead to much stronger correlations
364 between single-neuron activity and that of adjacent neurons as a population. The correlations
365 between single-neuron and population-neuron activities were calculated to examine this issue.
366 For each single-population correlation, the population-neuron activity was constructed from the
367 activity of all the other simultaneously recorded neurons (see Methods for details; Fig. 4A).
368 Population-neuron CCGs were generated by cross-correlating single-neuron spike trains with
369 population-neuron spike trains that were obtained by simply summing the spike trains of all the
370 other simultaneously recorded neurons. The center-peak incidences in the population-neuron
371 CCGs were 79% for IT neurons (149/189), 80% for V4 neurons (119/149), and 58% for V1
372 neurons (99/171; Fig. 4B). These incidences were significantly higher than those observed in
373 single-neuron CCGs (IT, $P = 3.1 \times 10^{-15}$, effect size = 0.45; V4, $P = 1.6 \times 10^{-76}$, effect size = 0.51;
374 V1, $P = 1.2 \times 10^{-71}$, effect size = 0.49, chi-square test; see Fig. 1A). These results suggest that the
375 relationship between single-neuron spiking activity and the activity of adjacent neurons as a
376 population is stronger than that between pairs of single neurons. The center-peak incidence in
377 population-neuron CCGs differed across the three cortical areas ($P = 2.4 \times 10^{-6}$, effect size = 0.43,
378 chi-square test), indicating that the relationship between single-neuron and population-neuron
379 activities differed among cortical areas; *i.e.*, the correlations between single-neuron and
380 population-neuron spiking activities were weaker in V1 than in V4 or IT.

381

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***** Figure 4 near here *****

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Consistent with the higher incidences of peaks in population-neuron CCGs than in single-neuron CCGs, population-neuron signal and noise correlations were stronger than their single-neuron counterparts. Population-neuron signal correlation was 0.25 (median) for IT ($n = 141$), 0.19 for V4 ($n = 86$), and 0.26 for V1 ($n = 107$; Fig. 4C). Population-neuron signal correlation was stronger than single-neuron signal correlations in all three cortical areas (IT, $P = 3.3 \times 10^{-14}$, effect size = 0.20; V4, $P = 3.6 \times 10^{-7}$, effect size = 0.18; V1, $P = 1.4 \times 10^{-8}$, effect size = 0.17, Mann-Whitney U-test; see Fig. 2B). Population-neuron noise correlation was 0.11 (median) for IT ($n = 141$), 0.07 for V4 ($n = 86$), and 0.04 for V1 ($n = 107$; Fig. 4D), and was higher than single-neuron noise correlation in all three cortical areas (IT, $P = 2.4 \times 10^{-25}$, effect size = 0.27; V4, $P = 1.5 \times 10^{-15}$, effect size = 0.27; V1, $P = 7.0 \times 10^{-12}$, effect size = 0.20; Mann-Whitney U-test; see Fig. 2D). These results suggest that single-neuron responses are much more similar to the averaged responses of adjacent neurons than to the responses of adjacent single neurons. Population-neuron signal correlation did not differ among the three regions ($P = 0.051$, Kruskal–Wallis test; effect size, 0.14 for IT-V4, 0.02 for IT-V1, 0.16 for V4-V1), whereas population-neuron noise correlation did ($P = 8.9 \times 10^{-10}$, Kruskal–Wallis test; effect size, 0.18 for IT-V4, 0.40 for IT-V1, 0.27 for V4-V1).

Next, analyses examined whether single/population pairs with higher peaks in population-neuron CCGs tended to show higher population-neuron signal and noise correlations.

The peak height of population-neuron CCGs correlated positively with population-neuron signal

correlation in IT and V4, but not in V1 (IT, $r = 0.389$, $P = 1.83 \times 10^{-6}$; V4, $r = 0.288$, $P = 0.0071$;
V1, $r = -0.0041$, $P = 0.967$, test for independence; Fig. 4E). V1 pairs had significantly weaker
correlation than IT pairs (V1-IT, $P < 0.01$; V1-V4, $P = 0.04$; V4-IT, $P = 0.41$, test for the
similarity of two independent correlation coefficients). In all three cortical areas, the peak height
of population-neuron CCGs correlated positively with population-neuron noise correlation (IT, r
 $= 0.617$, $P = 3.58 \times 10^{-16}$; V4, $r = 0.617$, $P = 2.57 \times 10^{-10}$; V1, $r = 0.400$, $P = 1.95 \times 10^{-5}$, test for
independence; Fig. 4F). The relationship between the peak height of population-neuron CCGs
and population-neuron noise correlation did not differ among cortical areas (IT-V4, $P = 0.99$;
IT-V1, $P = 0.02$; V4-V1, $P = 0.04$).

Discussion

The present study aimed to clarify whether the structures of spiking-activity correlations differ
among hierarchically organized visual cortical areas of macaque monkeys. Among IT, V4, and
V1, IT pairs showed the highest incidences of center peaks in their CCGs, whereas V1 pairs
showed the lowest. The strength of signal correlations, however, did not differ among the three
cortical areas. Correlation between CCG-peak height and signal correlation was stronger in IT
than in V1. Analyses of population-neuron activity revealed a similar tendency. Thus, the
activity correlations between single neurons, as well as those between single neurons and the
surrounding population, differed among cortical areas.

Each cortical area has unique local neuronal circuitry

The incidence of center peaks in the CCGs differed among cortical areas, with IT

425 pairs showing the highest incidences and V1 pairs the lowest. Three possible confounding
 426 factors that might affect the estimated incidences of center peaks were considered. One is the
 427 difference in spike counts used for cross-correlation analysis among the three cortical areas (IT,
 428 509–19,906; V4, 521–24,332; V1, 500–11,752). Reanalysis of the incidences of neurons that
 429 emitted spikes in a limited range (500–12,000 spikes) confirmed the result, *i.e.*, center-peak
 430 incidence was highest for IT pairs (13.8%, 266/1,924), in-between for V4 pairs (10.0%,
 431 176/1,762), and lowest for V1 pairs (4.6%, 103/2,261). A second possible confounding factor is
 432 the distance between paired neurons. However, this is a non-issue because the estimated
 433 neuron-to-neuron distances did not differ among the three cortical areas ($P = 0.434$,
 434 Kruskal–Wallis test). A third possible confounding factor is underestimation of peak incidences
 435 due to the spike-overlapping problem. To circumvent this problem, the incidences of center
 436 peaks were compared only using neurons that were separated by more than five probes, and thus
 437 did not suffer from the spike-overlapping problem. This analysis confirmed the result; *i.e.*, the
 438 center-peak incidence in CCGs were highest for IT pairs (7.5%, 105/1,399), in-between for V4
 439 pairs (6.6%, 80/1,204), and lowest for V1 pairs (4.2%, 62/1,484). From the above analyses, the
 440 incidence of center peaks in CCGs can be concluded to differ among the three cortical areas.

441 Because center peaks in the CCGs can be interpreted as a sign of common input onto
 442 paired neurons (Perkel et al., 1967), the degree of input sharing can be inferred to change
 443 systematically along the ventral visual cortical pathway. The systematic changes in the
 444 incidence of CCG center peaks is consistent with the systematic changes in morphological
 445 properties along the pathway; *i.e.*, dendrites and axon terminal arbors occupy a larger area in
 446 later-stage visual cortical areas than those in the primary visual cortex (Blasdel and Lund, 1983;

447 Amir et al., 1993; Saleem et al., 1993; Elston et al., 1999; Tanigawa et al., 2005). These
448 morphological properties allow IT neurons to share inputs with many other neurons. The higher
449 degree of input sharing observed in IT cortex may contribute to generating selective responses
450 to complex objects by integrating a variety of visual cues (Gross et al., 1972; Perrett et al.,
451 1982; Desimone et al., 1984; Tanaka et al., 1991; Tamura and Tanaka, 2001; Tamura et al.,
452 2016).

453 Despite the differences in the organization of common inputs, signal correlation did
454 not differ among cortical areas. This result points to the possibility that the relationship between
455 the organization of neuronal circuitry and the similarity in stimulus preferences differed among
456 cortical areas. Indeed, correlation between CCG-peak height and signal correlation differed
457 among cortical areas and was stronger in IT than in V1. V1 neurons share stimulus preferences
458 without sharing inputs, whereas IT neurons share stimulus preferences precisely through their
459 shared inputs. Broad peak widths in the CCGs of IT-neuron pairs are likely to be a basis for the
460 stronger relationship between CCG-peak height and signal correlations.

461 Although incidence of CCG center peaks for paired single-neuron activity
462 (single/single CCG peaks) in the three cortical areas was generally low (< 14%), incidence in
463 population CCGs (single/population CCG peaks) was high (> 58%), meaning that weak
464 pairwise single-neuron correlations led to much stronger correlations between single-neuron and
465 population-neuron activity. The higher incidence of single/population CCG peaks than
466 single/single CCG peaks can be explained by two alternative scenarios. One possible scenario
467 (democratic) is that all neurons contribute to the correlated spiking activity, but each contributes
468 only a small fraction (Fig. 5A). In this scenario, weak input sharing across neurons in a

469 population generates peaks in population CCGs. The other scenario (despotic) is that only one
 470 or a few neurons contribute to the correlated activity (Fig. 5B). In this scenario, strong input
 471 sharing between only two or a few neurons generates peaks in population CCGs. Our
 472 preliminary analysis suggests that the first scenario (democratic) is likely because in most cases,
 473 removing spike trains one-by-one did not alter the shape of the population CCGs (IT, 149/149;
 474 V4, 115/119; V1, 98/99).

475

476 *Neuron populations in each cortical area encode information in a unique manner*

477 Signal correlations and noise correlations obtained in the present study are similar to
 478 those obtained in previous studies from monkeys given anesthesia as well as awake monkeys
 479 (Gawne and Richmond, 1993; Gawne et al., 1996; Kohn and Smith, 2005; Tamura et al., 2005;
 480 Kreiman et al., 2006; Smith and Kohn, 2008; Cohen and Maunsell, 2009; Kotake et al., 2009;
 481 Mitchell et al., 2009; Sato et al., 2009; Ecker et al., 2010; Smith and Sommer, 2013; Ecker et al.,
 482 2014; Tamura et al., 2014; Okun et al., 2015; see Cohen and Kohn, 2011 for review). Recently,
 483 Ecker et al. (2014) reported that opioid anesthesia induced coordinated fluctuations in neuronal
 484 activity and enhanced noise correlation (see also Goris et al., 2014). However, in the present
 485 study in which animals were given fentanyl citrate, noise correlations were generally low
 486 (0.009-0.034). The different results might be related to differences in the dosage of fentanyl
 487 citrate, as pointed out by Ecker et al. (2014). Several other factors also affect the coordinated
 488 fluctuations of neural activity (Schulz et al., 2015). These confounding factors make inter-area
 489 comparisons of results from different studies difficult (Cohen and Kohn, 2011).

490 Because noise correlation relates to the information-encoding ability of paired

neurons (Averbeck et al. 2006; Cohen and Kohn, 2011; Franke et al., 2016), differences in noise correlation across cortical regions suggest that representations of visual information by populations of local neurons changes systematically along the ventral visual pathway. Further, because synchronous activity encodes stimulus related information (Singer and Gray, 1995; Diesmann et al., 1999; Hirabayashi and Miyashita, 2005; Zandvakili and Kohn, 2015), differences in incidences in synchronous activity, *i.e.*, CCG peaks, across cortical regions suggest that representations of information via synchrony also changes systematically along the ventral visual pathway.

Differences in CCG peak-widths may relate to differences in the information integration window. Peak-widths changed systematically along the ventral visual pathway. IT pairs had the broadest CCG peaks and V1 pairs had the narrowest peaks among the three cortical areas, as expected from a theoretical study (Tanimoto et al., 2006). A longer temporal receptive window in later-stage cortical areas has been reported (Hasson et al., 2008; Honey et al., 2012). A longer integration window is beneficial for integrating a variety of visual cues, which are likely to be processed in different speeds. The differences in temporal CCG properties might derive from the differences in temporal firing properties (Gochin et al., 1991; Murray et al., 2014), number of inputs (Krüger and Aiple, 1988), types of inputs (excitatory versus inhibitory; Perkel et al., 1967), the effects of non-sensory inputs (Goris et al., 2014), or their combinations. Currently, the factors that contribute to the difference are unknown.

From the present results, each cortical area can be inferred to have unique neural circuitry and information representation. Computations or algorithms performed by neuronal circuitry have been repeatedly reported to be shared among cortical areas (Creutzfeldt, 1977;

513 Douglas and Martin, 2004; Carandini and Heeger, 2012). However, if we assume that neural
514 circuitry and information representation are optimized for specific computations, differences in
515 neural circuitry and representation among cortical areas might suggest that each cortical area
516 performs unique computations and canonical view of cortical computations should be
517 reexamined.

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674 **Figure Legends**

675 **Figure 1.** Cross-correlation analysis of spiking activity for paired neurons recorded from IT, V4,
676 and V1. **A**, Comparison of the proportions of pairs with significant CCGs center-peaks among
677 IT (n = 2,082), V4 (n = 1,797), and V1 (n = 2,261). **B-D**, Shift-corrected CCGs with significant
678 center peaks for IT (B, top, n = 280), V4 (C, top, n = 166), and V1 (D, top, n = 86). Each line in
679 a color plot corresponds to individual CCG, which was normalized with its CCG-peak
680 amplitude and color coded. Color coded CCGs were sorted according to width index. Average
681 shift-corrected CCGs across the CCGs of pairs with significant center-peaks are shown for IT
682 (B, bottom), V4 (C, bottom), and V1(D, bottom). The horizontal dashed line is the baseline and
683 the vertical dashed line is the zero-time delay. The time constant (τ) that corresponds to the time
684 delay until the amplitude decreases to 37% of the peak is provided in the plots. **E**, Comparison
685 of the width index of CCG-center peak among IT, V4, and V1. The index takes a value of one
686 for neuron pairs with sharp peaks one-bin in width and takes larger values for neuron pairs with
687 much broader peaks. The center of each box plot is the median, and the right and left of the box
688 are the upper and lower quartiles, respectively. Attached whiskers connect the most extreme
689 values within 150% of the interquartile range from the end of each box.

690

691 **Figure 2.** Signal correlation and noise correlation of paired neurons recorded from IT, V4, and
692 V1. **A**, Frequency distribution of signal correlation for IT pairs. Open column, significant
693 correlation ($P < 0.01$, test of independence). Filled column, non-significant correlation. Vertical
694 dashed line, zero signal correlation. **B**, Comparison of signal correlation across IT, V4, and V1.
695 Vertical dashed line, zero signal correlation. **C**, Frequency distribution of noise correlation for

IT pairs. Other conventions are as in A. **D**, Comparison of noise correlation across IT, V4, and V1. Other conventions are as in B.

Figure 3. Relationships between CCG-peak height and signal correlation or noise correlation. **A-C**, Relationship between CCG-peak height and signal correlation in IT (A), V4 (B), and V1 (C) pairs. CCG-peak heights are plotted on a logarithmic scale. Each point represents one neuron pair. Each color represents pairs obtained from a single recording session. The correlation coefficient (r) between CCG-peak height and signal correlation is provided in the plots. **D**, Comparison of the correlation coefficient (r) between CCG-peak height and signal correlation across IT, V4 and V1. Attached bars are 95% confidence intervals. **E-G**, Relationship between CCG-peak height and noise correlation in IT (E), V4 (F), and V1 (G) pairs. Other conventions are as in A-C. **H**, Comparison of correlation coefficient (r) between CCG-peak height and noise correlation across IT, V4, and V1. Other conventions are as in D.

Figure 4. Relationships between single-neuron and population-neuron activities. **A**, Construction of population spike trains (population) from spike trains of three neurons (A, B and C). **B**, Comparison of proportions of neurons with significant ($P < 0.0001$, binomial test) center peaks in population CCGs (pCCGs) for IT ($n = 189$), V4 ($n = 149$), and V1 ($n = 171$). **C**, Comparison of population signal correlation (pSignal correlation) for IT, V4, and V1. Vertical dashed line, zero correlation. **D**, Comparison of population noise correlation (pNoise correlation) across IT, V4, and V1. Other conventions are as in C. **E**, Comparison of correlation coefficient (r) between population CCG-peak height and population signal correlation across IT,

718 V4, and V1. Attached bars are 95% confidence interval. Vertical dashed line, zero correlation. **F**,
 719 Comparison of correlation coefficient (r) between population CCG-peak height and population
 720 noise correlation across IT, V4, and V1. Other conventions are as in E.

721

722 **Figure 5.** Two possible scenarios that explain the higher incidences of peaks in CCGs for
 723 single/population pairs than for single/single pairs. Here, the spike train of a single neuron
 724 (single) was correlated with that of the neuron population (population) derived from neuron A-C.
 725 **A**, One possible scenario (democratic) is that all neurons contribute to the correlated firings, but
 726 their contributions are small. Vertical bars represent timings of spikes. Red and black bars
 727 represent correlated and independent spikes, respectively. Correlated spikes (red vertical bars)
 728 are observed in all the neurons. **B**, The other scenario (despotic) is that only one or a few
 729 neurons (here, neuron A) contribute to the correlated activity. Correlated spikes (red vertical
 730 bars) are observed only in neuron A. Other conventions are as in A.

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Figure 1
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