High noise correlation between the functionally connected neurons in emergent V1 microcircuits.

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Author Contributions

VB did the experiments, analyzed the data and wrote the manuscript. LB SC and NC participated in the experiments and analyses of data. JR contributed to the analyses of data. VB and SM conceived the idea of study. SM contributed to data analyses and manuscript writing.

Conflict of interest

The authors report no conflict of interest.

Abstract

Neural correlations (noise correlations and cross-correlograms) are widely studied to infer functional connectivity between neurons. High noise correlations (Rsc) between neurons have been reported to increase the encoding accuracy of a neuronal population; however, low noise correlations have also been documented to play a critical role in cortical microcircuits. Therefore, the role of noise correlations in neural encoding is highly debated. To this aim, through multi-electrodes, we recorded neuronal ensembles in the primary visual cortex of anesthetized cats. By computing cross-correlograms (CCGs), we divulged the functional network (microcircuit) between neurons within an ensemble in relation to a specific orientation. We show that functionally connected neurons systematically exhibit higher noise correlations than functionally unconnected neurons in a microcircuit that is activated in response to a particular orientation. Furthermore, the mean strength of noise correlations for the connected neurons increases steeply than the unconnected neurons as a function of the resolution-window used to calculate noise correlations. We suggest that, neurons that display high noise correlations in emergent microcircuits feature functional connections which are inevitable for information encoding in the primary visual cortex.

Keywords: Cell-assembly, Cross-correlation (CCG), Functional connection, Noise correlation (Rsc)

Introduction

There is mounting evidence that understanding of information encoding in brain requires studying the correlation (noise correlation or Rsc; cross-correlations or CCG) between neurons (Perkel et al. 1967; Alloway and Roy 2002; Bach and Kruger 1986; Zohary et al. 1994; Averbeck and Lee 2003; Barthó et al. 2004; Uhlhaas et al. 2009; Cohen and Kohn 2011; Graf et al. 2011; Cotton et al. 2013; Cossell et al. 2015). Rsc is the trial-by-trial Pearson correlation of the spike counts of two neurons in response to the same stimulus, and it simply gives us information about the degree to which trial-by-trial fluctuations are shared by a neuron pair (Averbeck et al. 2006; Cohen and Kohn 2011). On the other hand, a 'CCG' is a histogram of the firing rate of the target neuron with reference to the spiking of another neuron, and it provides the direction and type of functional link between neurons (Alonso and Martinez 1998; Barthó et al. 2004; Fujisawa et al. 2008; Bharmauria et al. 2014; Bharmauria et al. 2015). A peak offset from zero (quasi-

synchrony) in a 'CCG' indicates a putative excitatory or inhibitory connection, whereas a peak straddling zero (synchrony) signifies a common input to neurons (Perkel et al. 1967; Shadlen and Newsome 1998; Dong et al. 2008; Bachatene et al. 2012).

On one hand, many previous studies (in the visual cortex of different species) have reported high Rsc between neurons (Gawne et al. 1996; Kohn and Smith 2005; Gutnisky and Dragoi 2008; Cohen and Kohn 2011; Cotton et al. 2013; Cossell et al. 2015), suggesting that highly correlated neurons may share a great deal of sensory input (Zohary et al. 1994; Shadlen and Newsome 1998; Bair et al. 2001; Kohn and Smith 2005). On the other hand, decorrelated firing (low Rsc) has also been observed in V1 microcircuits (Ecker et al. 2010; Renart etl. 2010), implying that highly correlated variability may be detrimental to population coding (Zohary et al. 1994; Sompolinsky et al. 2001). Investigators have also reported in V1 that, a CCG between a neuronal pair fluctuates systematically with the stimulus (orientation) irrespective of low or high Rsc between them (Gawne et al. 1996; Bair et al. 2001; Reich et al. 2001; Kohn and Smith 2005). Thus, a contentious debate persists concerning the precise nature of Rsc in microcircuits (Cohen and Kohn 2011; Averbeck et al. 2006)

A major factor while calculating Rsc is the counting window (resolution-window, as we name it) that is employed to compute Rsc (Cohen and Kohn 2011; Hansen et al. 2012; Schulz et al. 2015). Shorter windows may underestimate the true Rsc between neurons, whereas bigger windows may add artificial correlation between spike-trains (Cohen and Kohn 2011; Hansen et al. 2012).

Recently, we have shown that a salient functional network (microcircuit) is activated within an ensemble (Bharmauria et al. 2015b, in press) in a characteristical 50-ms window of opportunity, wherein neurons cooperate synergistically exhibiting augmented power of gamma oscillations (Bharmauria et al. 2014; Bharmauria et al. 2015a) . In the current investigation, we report that, in such an emergent microcircuit framed by an ensemble (simultaneously recorded neurons from a microelectrode), the connected pairs exhibit significantly higher Rsc than the unconnected pairs at all the resolution-windows. Moreover, consistent with the previous findings (Gawne et al. 1996; Bair et al. 2001; Reich et al. 2001; Kohn and Smith 2005), the value of Rsc between a pair is independent of the presented orientation in an ensemble irrespective of the activation or inactivation of a functional connection between them at that orientation. To

our knowledge, this investigation is the first to systematically investigate the connected and unconnected pairs based on correlations (Rsc and CCG) in a microcircuit. This report further corroborates the earlier finding (Cossell et al. 2015) that, high Rsc between the strongly connected neurons carries well defined and structured information in microcircuits. However, importantly, Rsc has to be calculated in optimal resolution-windows to extract meaningful information from these microcircuits. We suggest that highly correlated (stable or strong connections) neurons are major junctions of information routing in quasi-simultaneously active cohorts of neurons.

Materials and methods

Ethical approval

Five adult animals (Cats) were prepared for electrophysiological recordings in the primary visual cortex (layer II/III, area 17), as per the guidelines of Canadian Council on Animal Care and approved by the Institutional Animal Care and Use committee of Université de Montreal. The procedure is as below.

Animals, anaesthesia and surgical procedures

Animals premedicated with acepromazine maleate (Atravet, Wyeth-Ayerst, Guelph, ON, Canada; 1 mg/kg, intramuscular) and atropine sulphate (ATRO-SA, Rafter, Calgary, AB, Canada; 0.04 mg/kg, intramuscular) were anesthetized with ketamine hydrochloride (Rogarsetic, Pfizer, Kirkland, QC, Canada; 25 mg/kg, intramuscular). The cats were then paralyzed with 40 mg and maintained with 10 mg/kg/h of gallamine triethiodide (Flaxedil, Sigma Chemical, St. Louis, MO, USA; intravenous) administered in 5% dextrose lactated Ringer's nutritive solution. General anesthesia was maintained by artificial ventilation with a mixture of N_2O/O_2 (70:30) supplemented with 0.5% isoflurane (AErrane, Baxter, Toronto, ON, Canada). Electroencephalogram, electrocardiogram, rectal temperature and end-tidal CO_2 partial pressure were monitored throughout the experiment, and kept in physiological ranges. The pupils were dilated with atropine sulfate (1%, Isopto-Atropine; Alcon, Mississauga, Ontario, Canada) and the nictitating membranes were retracted with phenylephrine hydrochloride (2.5%, Mydfrin, Alcon). The loci of the area centrales were inferred from the position of the blind spots which were opthalmoscopically focused and projected

onto a translucent screen. At the end of the experiment, the cats were euthanized intravenously with a dose (0.5 mL/kg) of Sodium Pentobarbital (CEVA, Sante Animale).

Visual stimulation

Monocular stimulation was done. The multi-unit receptive fields (RF) were mapped as the minimum response field (Barlow et al. 1967) by using a hand-held ophthalmoscope after clearly detectable activity had been obtained. These preliminary tests revealed qualitative properties such as dimensions, velocity-preference, orientation, and directional selectivity of neurons. Visual stimuli were generated with a VSG 2/5 graphic board (Cambridge Research Systems, Rochester, England) and displayed on a 21-inch monitor (Sony GDM-F520 Trinitron, Tokyo, Japan) placed 57 cm from the cat's eyes, with 1024 × 768 pixels, running at 100-Hz frame refresh. The blank screen was uniformly gray (~35 Cd/m^2). Contrast was set at 80%. Mean luminance was 40 cd/m^2. Optimal spatial and temporal frequencies were set at 0.24 cycles/deg and a range of 1.0–2.0 Hz, respectively, where V1 neurons are driven maximally by sine-wave drifting gratings (Bardy et al. 2006). The tested orientations were presented in a random order. Each drifting grating was presented in blocks of 25 trials (each trial lasted 4.1 s) with varying inter-stimulus (1–3 s) intervals during which no stimulus was presented (Fig. 1a). Thus the presentation of a stimulus lasted 180 s (with all trials and inter-stimulus intervals).

Electrophysiological recording and single-unit selection

Multi-unit activity in the primary visual cortex was recorded by a tungsten multi-electrode (Frederick Haer & Co, Matrix Electrode; the multi-electrode had four columns, and each column had one row). The recordings were performed at locations 410 or 820 μm apart (Fig. 1b). Twelve recordings (24 sites) were done across all cats either in the left or the right hemisphere. Recordings were performed in the supragranular layers (cortical depth < 1000 μm; mean = 650 μm). The signal from the microelectrodes was amplified, band-pass filtered (300 Hz–3 kHz), digitized and recorded with a 0.05 ms temporal resolution (Spike2, CED, Cambridge, England). Spike sorting from the multi-unit signals was done. Neurons were discriminated on the basis of three criteria: 1) the spike-waveform difference 2) principal component analysis (PCA) showing well dissociated clusters 3) and auto-correlograms (ACG) showing no events

(indicative of the refractory period of neuron) at the central point (Csicsvari et al. 1998; Barthó et al. 2004; Bharmauria et al. 2014). The stability of each cell's activity across conditions was verified qualitatively by the visual control of the disposition of clusters and the shapes of waveforms. Cluster analysis was performed using Spike2, CED, Cambridge, England in a 3-dimensional plot. The isolation distance was calculated as the Mahalanobis distance. The Mahalanobis distance is the distance from the cluster center within which as many events belong to the other clusters as to the specified cluster (Harris *et al.*, 2001). In other words, given the multivariate data values for which the values in each variable are normally distributed around a mean, this measure allows to define boundaries of constant probability around the multi-dimensional center of the distribution. Thus, this estimation allows the separation of a cluster from the nearest cluster. Units within a Mahalanobis distance of 2.5 were considered for further analysis of the spike trains to reveal the functional connections between them. An example of dissociated spikes from multiunit activity is shown in Fig. 1c. The corresponding PCA and auto-correlograms are shown in Fig. 1d and Fig. 1e respectively.

Cross-correlogram (CCG) computation

Cross-correlogarms were computed (binwidth = 1 ms) between the neural activities of all the possible neuron pairs at all the applied orientations to reveal the functional connections. The raw CCGs were shift-corrected (one spike train shifted over one stimulus period) to eliminate the putative significant peaks due to the simultaneous stimulation of both cells during each trial (to remove the stimulus-evoked and locked components) (Perkel et al. 1967). A significant peak of 2 ms (two adjacent bins) or at least one significant bin (Alloway & Roy, 2002) was searched within a window of ± 5 ms offset from zero (excluding the ±1 ms bins around zero) in the shift-corrected CCG to reveal a functional connection between two neurons. The statistical threshold for the significant peak was set at 95%, and the probability (P) of the neuronal firing in a bin is calculated according to Abeles (1982). The details are present in Bharmauria et al (2014).

Calculation of noise correlation (Rsc)

Noise correlation represents the trial-by-trial Pearson correlation-coefficient between the simultaneous firing of two neurons in response to the presentation of an identical stimulus (Cohen and Kohn 2011). Rsc was calculated for the connected and unconnected pairs across all ensembles at one selected orientation

where the most number of connections were found. An optimal or near optimal orientation was chosen for closely tuned assemblies, whereas an orientation exhibiting maximum connections was selected for assemblies with wide orientation spreads. Rsc was calculated over all 25 trials for a neuron pair. The respective trials of the pair were correlated. The Rsc-computation was performed over three different counting windows (resolution-window) separately (5 ms, 25 ms and 50 ms). A resolution-window is the equally sized bin into which the whole trial duration is divided to perform the Rsc-computation. For example, in our case, a trial of 4 sec yielded 800 bins when the resolution-window was set at 5 ms.

Results

The aim of the current investigation was to systematically compare the noise correlation between the functionally connected (as revealed from the CCGs, see methods) and unconnected neuron pairs in V1 microcircuits activated within an ensemble. It is to be noted that, within the context of this paper, simultaneously recorded neurons from a microelectrode are termed an ensemble (that is, coactive neurons as Miller et al (2014) have defined them).It is to be underlined that a particular microcircuit activated within an ensemble at a specific orientation (for closely tuned ensembles an optimal or non-optimal orientation that exhibited numerous connections was chosen, and for distantly tuned ensembles an orientation that exhibited maximum connections was chosen) was selected to systematically compare the connected and unconnected neurons.. Across twenty four sites, 94 neurons were recorded; 62 functionally connected and 47 unconnected pairs were analysed.

Revealing the functional connection between neurons

Neurons in physical proximity share a great deal of peripheral input (Averbeck and Lee 2003; Shadlen and Newsome 1998), therefore, it is expected that they exhibit abundant functional connections with each other. Previously we have shown that a ‘signature’ functional network is framed by an ensemble contingent upon the presented orientation (Bharmauria et al. 2015b, in press). We computed CCGs to reveal these functional connections within an ensemble. A typical example of a connected and an unconnected neuron pair is shown in Fig. 2. Fig. 2a illustrates the raster plots of two simultaneously recorded neurons with respective waveforms as insets. Fig. 2b shows the CCG between the above spike trains (light green neuron is the reference), and the significant (the green background indicates the significance level, see methods) peak

off-set from zero (within 5 ms) indicates that the reference neuron projects onto the target neuron (Barthó et al. 2004; Bharmauria et al. 2015). The probability (P) of the peak that reflects the strength of connection is 0.016. The cumulative histogram of the target neuron (black curve above the CCG) further signifies that, once the reference neuron fires, it leads to an upsurge in the activity of the target neuron transiently. Fig. 2c illustrates the raster plots (waveforms as insets) of an unconnected pair (absence of the significant peak) as inferred from the CCG (light red neuron is the reference) in Fig. 2d. It is to be noted that the above three neurons (same target neuron in both cases) were recorded simultaneously from a microelectrode, thus constitute an ensemble.

High noise correlation between the functionally connected neurons in an assembly

Recently, in mouse visual cortex, it has been shown that highly correlated (Rsc) neurons are strongly connected to each other (Cossell et al. 2015). After computing CCGs that revealed the functional connections, we calculated Rsc for the connected and unconnected pairs in an ensemble (at a specific microcircuit) at different resolution-windows. Fig. 3 shows an example of Rsc-comparison between the connected and unconnected pairs in an ensemble (four simultaneously recorded neurons). The first matrix (Fig. 3a) illustrates the connectivity and the strength (colored scale) of the functional connections as divulged by CCGs. Out of the six possible pairs, three pairs (red-cyan; red-blue; blue-cyan) were connected, and the other three pairs were unconnected. It is to be noted that the matrix is symmetric along the diagonal (that is, the same connection is also represented on other side of diagonal). Fig. 3b shows the Rsc-values for the same pairs at 5-ms resolution-window (see methods). The Rsc-strength seems to be almost equivalent for all pairs. However, the Rsc-values for the respective pairs increased systematically as we increased the resolution-windows from 5-ms to 25-ms (Fig. 3c) to 50-ms (Fig. 3d). The strength of Rsc for the connected pairs increased steeply than the unconnected pairs. Fig. 3e further shows the difference in increase in Rsc for the connected (green curves) and unconnected pairs (red curves). For example, the Rsc values for the blue-cyan (connected) pair increased steeply from 0.02 at 5-ms to 0.16 at 25-ms to 0.19 at 50-ms window; whereas for the red-purple (unconnected) pair, the respective Rsc values were found to be 0.00, 0.01 and 0.04. On a microcircuit basis (Fig. 3f), the mean correlation (with SD) for the connected pairs increased from 0.02 ± 0.00 at 5-ms to 0.12 ± 0.03 at 25-ms to 0.14 ± 0.03 at 50-ms window; whereas, the corresponding values for the unconnected pairs were found to be 0.00 ± 0.00; 0.00 ± 0.13 and 0.04 ±

0.00. Both curves were significantly different (unpaired t-test, $p < 0.05$). In summary, in a microcircuit activated within an ensemble, the connected neuron pairs systematically carry high Rsc than the unconnected neurons, implying that neurons with high Rsc may be strongly related to the presented feature.

Strength of connection (P), noise correlation (Rsc) and resolution-window

Many investigators (Zohary et al. 1994; Graf et al. 2011; Hansen et al. 2012; Cossell et al. 2015) have suggested that high Rsc is directly related to the strength of the connection between neurons. We thus investigated how the probability of the peak (P) in the CCG might be related to Rsc between the same neurons. Fig. 4a depicts that there is no relation between P and Rsc when Rsc was calculated in a low (5ms) resolution-window, as the regression curve did not deviate significantly from zero ($p > 0.05$). However, when the similar analysis was performed at 25-ms (Fig. 4b) and 50-ms (Fig. 4c) windows, the regression curves significantly deviated from zero in either case ($p < 0.05$), thus, indicating that as the Rsc value increases, the peak-probability in the CCG tends to increase too. In short, this analysis points to the fact that Rsc has to be calculated in optimal resolution-windows to undermine the true correlation between the firing of two neurons. In other words, in optimal resolution-windows, it is possible to associate the strength of the connections (P) to Rsc; if Rsc is high, P is high too.

Rsc dynamics within a microcircuit in relation to the presented orientation

As discussed above, we have already shown that an ensemble frames a specific functional network (microcircuit) that is strictly related to the presented orientation (Bharmauria et al. 2015b, in press). We next examined the fluctuation of Rsc for the same neurons pairs in an ensemble (that is, from one microcircuit to another) as the orientation tilted in 22.5° steps. An example of an ensemble comprising four neurons (all neurons were tuned approximately to 90°) is shown in Fig. 5a. A specific network is activated at each presented orientation. The red-blue pair remains unconnected in all networks, exhibiting almost similar Rsc values (Fig. 5b). The red-green pair is connected at four orientations exhibiting high Rsc values, except at 135° where it displays a low Rsc value and displaying no connection. Interestingly, in other four pairs, neurons remained unconnected regardless of the high values of Rsc in these microcircuits. For example, the red-orange pair exhibited highest Rsc (0.17) at 45°, but failed to display a connection. This seems to be in line with previous reports (Gawne et al. 1996; Bair et al. 2001; Reich et al. 2001; Kohn

and Smith 2005) wherein investigators documented that the peak in CCG was orientation-dependent, whereas the respective Rsc of the involved neurons was independent of the tilt in orientation. Hence it appears that Rsc and CCGs have to be appropriately associated to each other in microcircuits. With this example and other analyses, we show that within an emergent microcircuit, the connected pairs always exhibit higher average Rsc values than the unconnected pairs (it is to be noted that in all the microcircuits, the connected pairs always had higher average Rsc then unconnected pairs).

Significant difference between the connected and the unconnected pairs

Finally, all the connected and unconnected pairs were pooled as separate groups to observe the global trend of variation of Rsc as a function of the resolution-window (Fig. 6). The mean Rsc (with SEM) for the connected pairs (n = 62) increased steeply from 5-ms to 25-ms to 50-ms window (0.02 ± 0.00 to 0.13 ± 0.01 to 0.18 ± 0.01 respectively) and significantly differed (respective values for the unconnected class were 0.00 ± 0.00; 0.01 ± 00 and 0.04 ± 00) from the unconnected pairs (n = 47) at every resolution-window (Kolmogorov-Smirnov test, $p < 0.05$). This coincides with previous reports (Hansen et al. 2012; Schulz et al. 2015), wherein they reported that noise correlation increased with the resolution-window. In summary, we may suggest that whenever two neurons in a "microcircuit" exhibit high Rsc, this may augur a functional connection between them.

Discussion

In this study, the noise correlation (Rsc) was systematically compared for the connected and the unconnected neuron pairs in V1 microcircuits. We found that Rsc-values were significantly higher and different for the connected neuron pairs than the unconnected pairs. Further, we found that the peak-probability (indicative of strength of the connection) in the CCG increases with Rsc at higher resolution-windows.

Methodological considerations

The current experiments were done on anaesthetized cats and we have already shown that the disclosed functional connections are strongly related to the presented stimulus rather than the spontaneous fluctuations in the brain — the proportion of connections was more at stimulus conditions than at

spontaneous activity; the gamma power was high at stimulus presentation than at spontaneous oscialltions (Bharmauria et al. 2014; Bharmauria et al. 2015a, Bharmauria et al. 2015b, in press). Many investigations have reported that nearby neurons carry high noise correlations between them (Zohary et al. 1994; Kohn and Smith 2005; Graf et al. 2011; Cossell et al. 2015). One may also argue that high noise correlation between the connected neurons in current investigation might be attributed to the artificial binning of spikes in wider resolution windows, but if it were the case we would not have obtained such trendy difference between the connected and the unconnected pairs. Moreover, Cohen and Kohn (2011) have suggested that noise correlation between the jittered spike trains (since the peaks in CCGs that revealed the functional connections were jittered in our case, that is, offset from zero) have to be calculated over higher resolution-windows and longer trial durations in order to capture the full strength of Rsc. Because we used higher resolution-windows and longer trial durations to calculate Rsc, we may infer that indeed the functionally connected neurons carry higher noise correlation between their spike trains in emergent cortical microcircuits.

Functional consequences

Recently, through calcium imaging and electrode recordings in slices of mouse V1 (Cossell et al. 2015), investigators have shown that nearby neurons exhibiting higher spike-count correlations are strongly connected to each other, and are predominantly responsible for feature encoding. We found that, in general, the strength of connections increases as a function of Rsc (although in higher resolution windows) between neurons. Thus, we may suggest that neurons with higher Rsc were strongly connected to each other and played a major role in stimulus processing.

Along the same lines (as suggested by Cossell et al. 2015), we may also suggest that in layer II/III, majority of the input to a strongly connected neuron (a reader neuron as postulated by Buzsáki, 2010) is provided by other neurons that share the similar tuning property as the reader neuron. Indeed, this investigation extends the work on ensembles (Miller et al. 2014; Reid et al. 2015; Bharmauria et al. 2015b), wherein authors have shown that same ensembles are active in response to the stimulus and even at spontaneous oscillations. We have already reported that a signature microcircuit is activated in such an ensemble that is strictly related to the presented stimulus (Bharmauria et al. 2015b). Reid et al (2015) documented that within the sequential

activation of ensembles in a Hebbian assembly, neurons fire with repeating firing patterns in an ensemble called 'doublet pathways'. Such recurring patterns of spiking activity were revealed through CCGs by us that were indicative of functional connections between neurons. Furthermore, building upon these investigations, herein, we show that within a particular microcircuit framed by an ensemble, the connected neurons systematically exhibit higher Rsc than the unconnected neurons. Moreover, we also report that, Rsc between neurons is independent of the presented orientation and the neurons may or may not exhibit connections from one orientation to another irrespective of the strength of Rsc. We suggest that the "inherent" temporal spiking pattern between neurons confers them almost equivalent Rsc along the presented orientations (Miller et al. 2014; Reid et al. 2015; Bharmauria et al. 2015b), but on occasions it may not be possible to reveal it through CCGs as the firing rate varies from one orientation to another. This study also relates to another recent study by Shimono and Beggs (2014), wherein they revealed such functional links in small clusters (3-6 neurons) using transfer entropy. Collectively, this may imply that every presented stimulus drives the ensemble in such a way that, a group of neurons (connected) within it covaries its responses systematically than the group of cells (unconnected) whose firings are independent of each other. Such strongly connected neurons feature a small proportion of connected neurons in distributed cortical circuits, and are implicated in major processing and transformation of information along the pathways. On the other hand, the weaker connections might be attributed to the plasticity based rules, that is, they can change (strengthen) contingent upon the input as has already been shown by Bharmauria et al (2015b, in press) — that a specific network between V1 neurons (layer II/III) is activated by a particular orientation. When the orientation changes, another network might be framed within the same ensemble — wherein, some connections may remain (strong) in relation to the previous orientation and other connections may become active.

From this study, we may conclude that, high noise correlations between neurons in cortical microcircuits augur functional interactions between them; however, it is important to calculate the noise correlation in appropriate resolution-windows to extract meaningful information from these simultaneously active local cohorts of neurons. This study along with our previous studies might form a premise for computational modeling to further our understanding of neural circuits.

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Legends

Fig. 1 A schematic of the experiment **(a)** Presentation of sine-wave drifting gratings in a random fashion. **(b)** Multi-unit recording in layer II/III (area 17) in the primary visual cortex. **(c)** An example of four neurons sorted from multi-unit activity recorded from a microelectrode. Each neuron has a distinct waveform and a well dissociated cluster. **(d)** Corresponding auto-correlograms (ACGs) for the isolated neurons.

Fig. 2 Inferring functional connectivity **(a)** Respective raster plots and perievent histograms of two simultaneously recorded neurons (waveforms as insets) from a microelectrode. **(b)** The cross-correlogram (CCG) between the spike trains of neurons (light green neuron is the reference) yielded a significant peak (P = 0.016) offset from zero (blue broken line), thus indicating that the reference neuron projects onto the target neuron. **(c)** Respective responses of two simultaneously recorded neurons (waveforms as insets) that did not exhibit a functional connection between them, as revealed from the non-significant CCG in **(d).** Note: The target neuron is same in both cases.

Fig. 3 High noise correlation between functionally connected neurons in a microcircuit **(a)** Functional connectivity matrix between four simultaneously recorded neurons from a microelectrode. Neurons along the x-axis project onto the y-axis neurons. Note: the matrix is symmetric along the diagonal, that is, the same connection is also represented on the other side of the diagonal. The colored scale stands for the strength of the connection. **(b,c,d)** Rsc- matrices of the same neurons at 5-ms, 25-ms and 50-ms resolution-windows respectively. The colored scale in '**b**' stands for all the matrices. **(e)** Noise-correlation as a function of the resolution-window for each pair in the microcircuit. The green curves represent the connected neuron pairs and the red lines correspond to the unconnected pairs. **(f)** Mean noise correlation for connected and unconnected neuron pairs as a function of the resolution window. The mean correlation is higher and significantly different for the connected pairs than the unconnected pairs (unpaired t-test, $p < 0.05$)

Fig. 4 Peak-probability (P), noise correlation (Rsc) and the resolution-window. **(a)** No relation is inferred between P and Rsc at 5-ms resolution-window as the regression curve did not deviate significantly from zero ($p > 0.05$). **(b,c)** 'P' and Rsc in relation to the 25-ms and 50-ms resolution windows. 'P' showed a significant relation with Rsc at both resolution windows ($p < 0.05$).

Fig. 5 An example of the dynamics of Rsc in an ensemble in relation to the presented orientation. **(a)** Activation of an emergent microcircuit contingent upon the presented orientation within an ensemble. **(b)**

Tabular matrix representing the mean Rsc (red box stands for the connected pair, blue box corresponds to the unconnected pair) for every pair at every presented orientation. $\bar{X}$ represents the mean.

Fig. 6 Global trend for the functionally connected (green) and unconnected (red) pairs. Functionally connected neurons exhibited significantly higher noise correlation than the unconnected neuron pairs at all the resolution windows (Kolmogorov-Smirnov test, $p <$ at 0.05).

Figure 1

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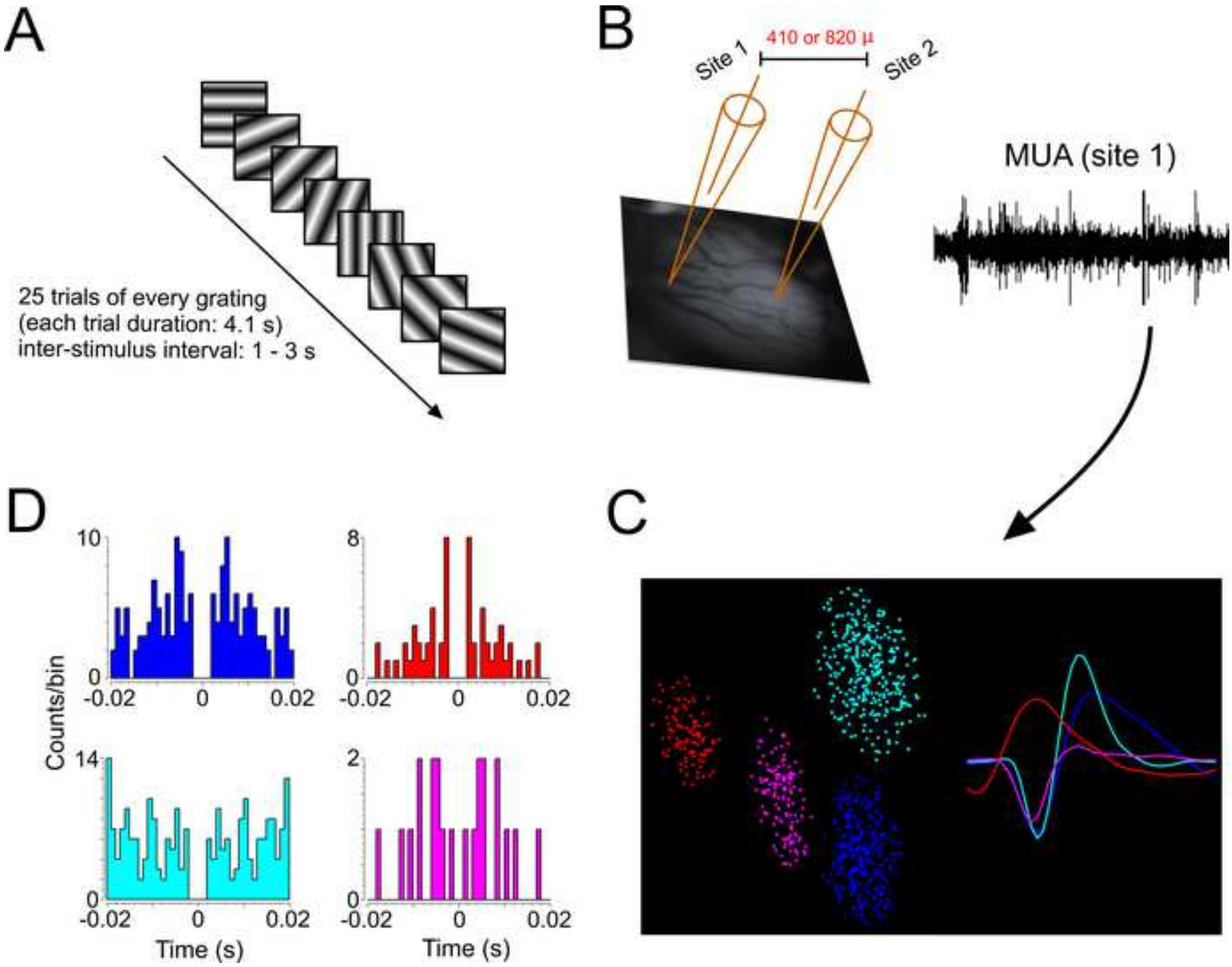

Figure 2

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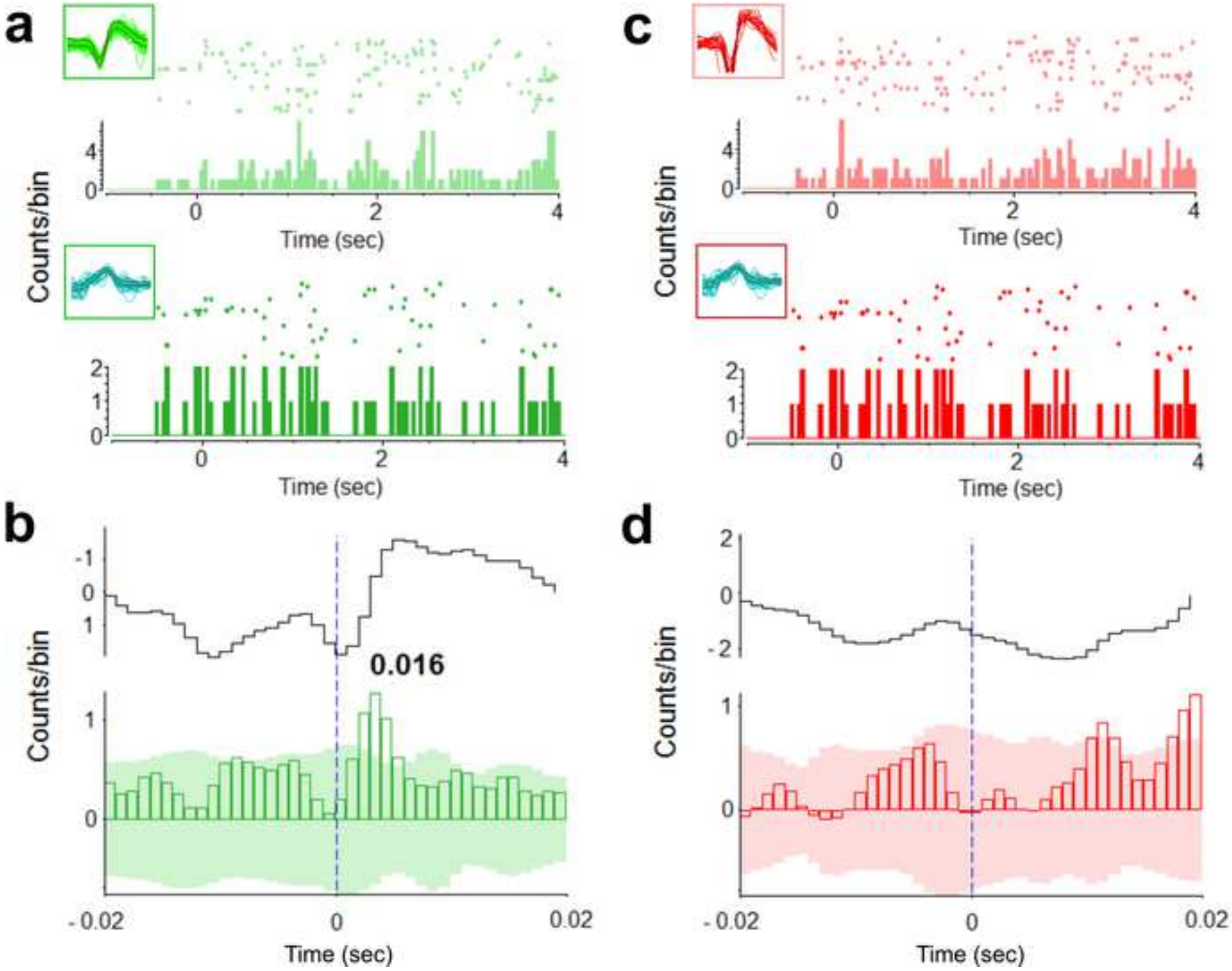

Figure 3

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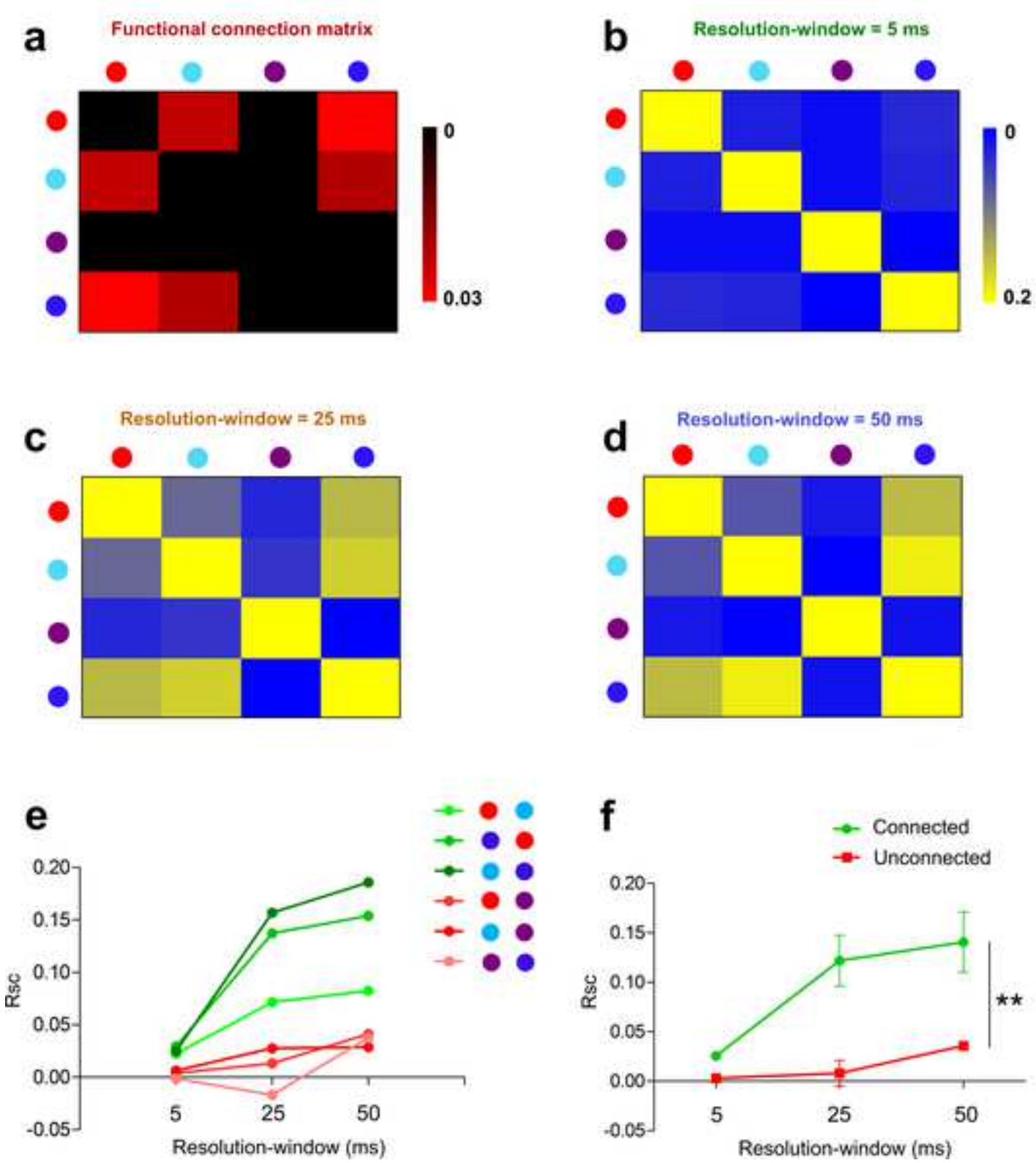

Figure 4

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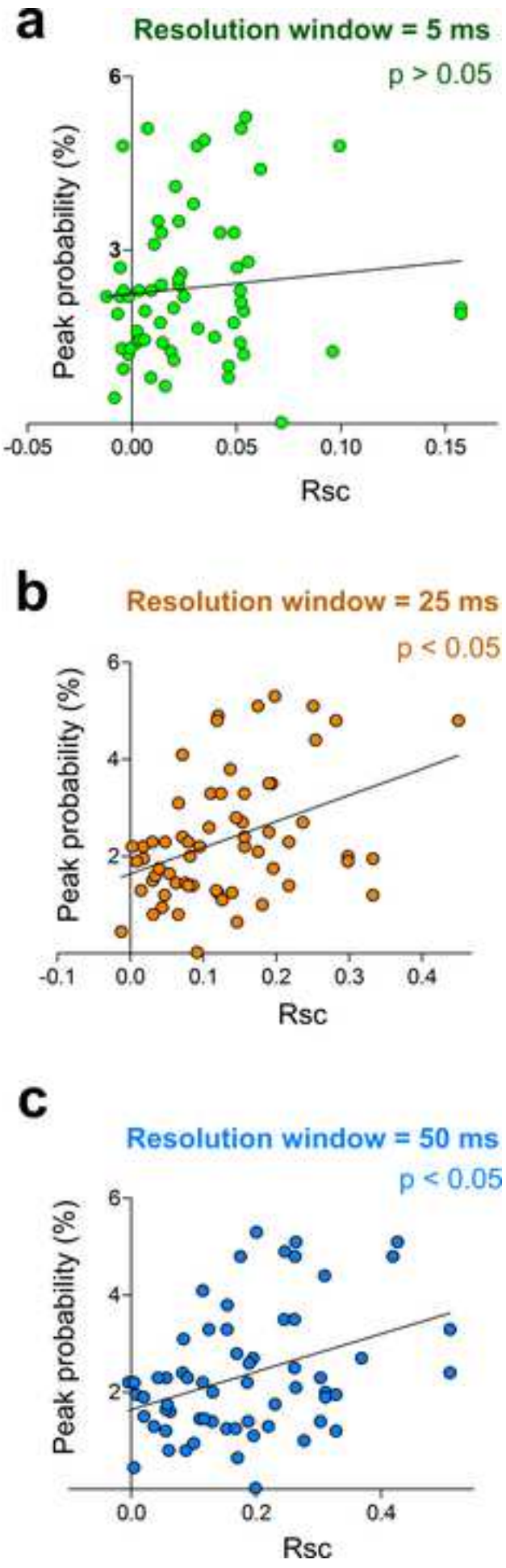
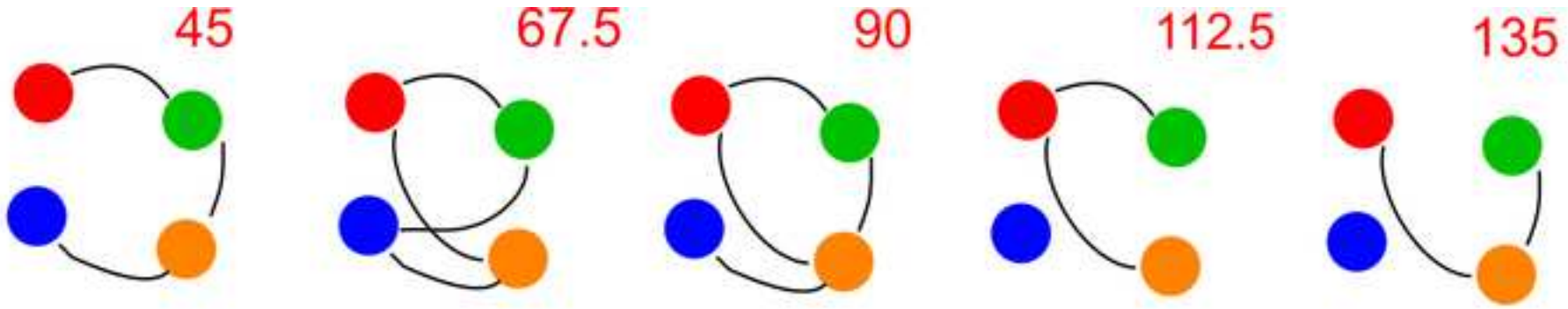


Figure 5

a



b

	45	67.5	90	112.5	135
● ●	0.08	0.11	0.09	0.10	0.07
● ●	0.14	0.11	0.11	0.17	0.07
● ●	0.17	0.15	0.13	0.10	0.12
● ●	0.14	0.15	0.04	0.08	0.12
● ●	0.21	0.15	0.08	0.14	0.03
● ●	0.15	0.14	0.13	0.09	0.17
Connected $\overline{X}$	0.17	0.14	0.11	0.14	0.15
Unconnected $\overline{X}$	0.13	0.12	0.06	0.10	0.07

Figure 6

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