Supplementary Information

Sensory stimulation shifts visual cortex from synchronous to asynchronous states

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Contents

1. Description of Supplementary Video

Continuous whole cell current clamp record of Vm from a V1 neuron and eye movements in the behaving macaque viewing sinusoidal drifting grating visual stimuli over multiple trials and inter-trial periods.

2. Grating-evoked responses and orientation tuning

In an example neuron, gratings at preferred and orthogonal orientations both evoked depolarization (Extended Data Fig. 1a, centre and right respectively) relative to the blank (Extended Data Fig. 1a, left). The depolarizations evoked by the preferred orientation were consistently suprathreshold and led to spiking. Depolarization of Vm and spike rate both decreased smoothly as grating orientation varied from preferred to orthogonal (Extended Data Fig. 1b). The relationship between Vm and spike rate R was well approximated by a threshold followed by a power law[1-3]:

$$R = \lfloor Vm - Vr \rfloor_{+}^{\alpha}$$

where + indicates rectification, Vr is the resting membrane potential, and α is the fitted exponent (Extended Data Fig. 1c). Orientation tuning curves for Vm (Extended Data Fig. 1d, left) and spike rate (Extended Data Fig. 1d, centre) had similar preferred orientations, but Vm was more broadly tuned than spike rate. The sharper tuning for spike rate is expected given the above power law relationship between Vm and spike rate. The orientation tuning predicted (Extended Data Fig. 1d, right) by applying the above power law relationship to the Vm orientation tuning curve (Extended Data Fig. 1d, left) was similar to the spike rate orientation tuning curve (Extended Data Fig. 1d, centre).

We assessed orientation selectivity[4,5] with an orientation selectivity index[6,7] (vector average = 1-circular variance). Across neurons, spike rate orientation tuning was sharper than Vm orientation tuning, as expected for power law relations between Vm and spike rate with exponents α ranging from approximately 2-5 (Extended Data Fig. 1e). Median Vm OSI was 0.26, and median spike rate OSI was 0.48, comparable to the median spike OSI of 0.39 (median circular variance of 0.61) obtained by Ringach et al[7].

We assessed the temporal modulation of neural responses by the Fourier component of the response with the same temporal frequency as the moving sinusoidal grating visual stimulus divided by the time averaged response[8] (F_1/F_0). This ratio was greater for spike responses (R_1/R_0) than for membrane potential (V_1/V_0), as expected for thresholded power law relations between Vm and spike rate with exponents α ranging from approximately 2-5 (Extended Data Fig. 1f).

3a. Estimation of Vm skew

In an asynchronous high conductance state, a neuron receives input from many uncorrelated excitatory and inhibitory neurons such that synaptic input is Gaussian, and a 'diffusion' approximation holds[9-14]. The near zero or negative skew in Vm when inputs are Gaussian is expected only for neurons in which spiking has been disabled. We therefore excluded portions of our traces in which spikes occurred in our estimates of Vm skew. Since we wish to demonstrate that the observed skewness is greater than would be expected for a range of Gaussian inputs consistent with an asynchronous high conductance state (see Supplementary Section 3b), we show that our procedure may underestimate, but is unlikely to overestimate skewness when a neuron receives such input.

Our procedure for estimating skewness is illustrated in Extended Data Fig. 2a on a simulated spiking neuron with Hodgkin-Huxley conductances (see Supplementary Section 3b, c). The neuron received Gaussian excitation (top traces, black) and Gaussian inhibition (top traces, red) (see Supplementary Section 3b for the parameter range simulated). With spiking disabled by setting all Hodgkin-Huxley conductances to zero, Vm was nearly Gaussian with skewness ζ = 0.24 (green trace and histogram). However, spiking resulted in artifactually high skewness ζ = 0.90, even though input was Gaussian (light blue trace and histogram). For estimating Vm skew, we therefore removed spikes by excluding from all traces a ±5 ms portion centred around each spike (dark blue trace), which removed the artifactually high skew, and resulted in an apparent skewness ζ = 0.27 (dark blue trace and histogram), close to the skewness obtained with spiking disabled (green trace and histogram).

This same procedure is illustrated on an example neuron from our data set in Extended Data Fig. 2b. Removing spikes reduced the skewness from ζ = 3.2 to ζ = 1.7, which was still above the skewness values expected for a range of Gaussian input (see Supplementary Section 3b for the parameter range simulated).

When this procedure was performed on simulated spiking neurons receiving a range of Gaussian input, the apparent skewness was always near or less than the skewness of the same neurons with spiking disabled, demonstrating that our procedure produces apparent Vm skews which are not overestimates of Vm skew when spiking is disabled (Extended Data Fig. 2c).

Extended Data Fig. 3 illustrates our procedure for estimating the skewness of Vm deviations from the mean during blank trials and during visual stimulation for Fig. 3d of the main text. For each neuron, the raw traces from each trial (Extended Data Fig. 3a) were bandpass filtered between 0.1 Hz and 100 Hz, and spikes were removed by excluding from all traces a ±5 ms portion centred around each spike, as described above (Extended Data Fig. 3b; see also Extended Data Fig. 2). Responses during each cycle of the drifting sinusoidal grating visual stimulus (i.e. cycle-by-cycle responses; Extended Data Fig. 3c, top grey traces) were then aligned and averaged to form the cycle-averaged response (Extended Data Fig. 3c, top black trace); responses during the first cycle of each grating were not used in the calculation of the cycle-averaged trace; blank trial traces were cycle averaged in the same way by considering the visual stimulus to be a sinusoidal drifting grating with zero contrast, but without omitting portions of traces from the first cycle of each grating. The cycle-averaged trace was subtracted

from each cycle-by-cycle response, leaving the Vm deviations from the mean (i.e. cycle-by-cycle residuals, Extended Data Fig. 3c, bottom grey traces). From the distribution of Vm (Extended Data Fig. 3c, top histogram) we have thus obtained the distribution of Vm deviations from the mean (Extended Data Fig. 3c, bottom histogram), from which the neuron's skewness of Vm deviations from the mean was estimated.

3b. Implication of Vm skewness

To estimate the range of skew values expected under Gaussian input, we simulated Gaussian input to neurons with spiking disabled with input resistances of 200 and 400 MΩ. Excitatory and inhibitory conductances were Ornstein-Uhlenbeck processes with 5 ms time constant. An Ornstein-Uhlenbeck process is a stationary Gaussian process that is a diffusion-like process with constant variance; the time constant of an Ornstein-Uhlenbeck process describes the width of its autocorrelation function; a 5 ms time constant is similar to that used in previous models of neurons in a high conductance state[15]. Mean Gaussian excitatory conductance was 7.5 nS, 10 nS, 12.5 nS or 15 nS; the standard deviation of the excitatory conductance was 1/5 or 1/10 the mean excitatory conductance; all neurons received Gaussian inhibition such that the mean total excitatory and inhibitory conductance was either 10 nS, 20 nS or 40 nS; the standard deviation of the inhibitory conductance was 1/5 or 1/10 the mean inhibitory conductance. Standard deviations that are 1/5 the mean are near the upper end of the biologically plausible range, because larger standard deviations lead to unphysiological negative conductances. We further restricted analysis to parameter combinations, which when spiking was enabled, resulted in spike rates less than 40 Hz, because we did not observe any spike rates greater than 40 Hz during blank trials.

In the simulated neurons receiving Gaussian input (see below), all but one of the above parameter combinations produced skewness values less than 0.5, and the greatest skewness was 0.6 (Extended Data Fig. 2c, horizontal axis). As the median apparent skew in our data set is 0.7 (Main Fig. 2f), at least half of the neurons in our data set probably do not receive Gaussian input within above parameter range, but receive input with a significant correlated input component. This analysis assumes a single compartment neuron model, as do network models of asynchronous high conductance states[9-11,16,17]. Neurons whose somatic membrane potential is strongly affected by dendritic voltage-gated channels may display other membrane potential distributions.

We note that skewness values less than 0.6 are also consistent with input that has a significant correlated input component[13,18-20], but skewness values alone are not able to distinguish between such input and purely Gaussian input. Similarly, skewness values less than 0.6 do not imply a small Vm-threshold distance.

To demonstrate this we re-present data from the main text to show the joint distribution of Vm-to-threshold distance and skewness during blank trials (Extended Data Fig. 4a). Vm-threshold distance is the primary indicator from the joint distribution that V1 during fixation in the absence of visual stimulation, is not in a high conductance state in which neurons receive

nearly Gaussian input and Vm hovers below spike threshold. The low skewness of some neurons does not imply that their Vm-threshold distance is small, as there are neurons in which their Vm-threshold distance is large even though their skewness is considerably lower than the median skewness of 0.7. Skewness is a complementary indicator which suggests that in addition to a large Vm-threshold distance, at least half of the neurons in our data set receive input with a significant correlated input component. For completeness, we also show the joint distribution of Vm-to-threshold distance and skewness during preferred orientation trials (Extended Data Fig. 4b), which indicates, relative to blank trials, decreased Vm-threshold distance due to stimulus-evoked depolarization, as well as reduced skewness consistent with input that is more Gaussian.

3c. Simulation details

Parameters for the neuron with Hodgkin-Huxley conductances were adapted from Destexhe et al (2001)[15] and Pospischil et al (2008)[21]. Neurons received Gaussian excitatory and inhibitory currents as indicated in section 3b. Simulations were carried out with Brian[22,23]. We list the simulation parameters, followed by the code.

Simulation parameters

Area = 12 000 X 10^{-12} m^2 or 24 000 X 10^{-12} m^2
Membrane capacitance, Cm = 1 µF cm^{-2} . Area
Leak conductance, g_l = 2.05e-5 S cm^{-2} . Area
Leak reversal potential, E_l = -70.3*mV
Potassium reversal potential, E_K = -90*mV
Sodium reversal potential, E_{Na} = 50*mV
Hodgkin-Huxley sodium conductance coefficient, g_{Na}= 0.056 S cm^{-2} . Area
Delayed rectified potassium conductance coefficient, g_{Kd} = 0.006 S cm^{-2} . Area
Threshold parameter, V_T= -56.2 mV
Synaptic excitation reversal potential, E_e = 0 mV
Synaptic inhibition reversal potential, E_i = -75 mV

Code

```
from brian import *
from brian.library.random_processes import *

def VmDistModel3HHN(filenumber,area,geave,giave,gestd,gistd):

    # Parameters
    # Neuron parameters from Pospischil et al, Biol Cybern, 2008
    # RS neuron in Fig 2A, but without slow non-inactivating K+ current
    # Synaptic parameters adapted from Destexhe et al, Neuroscience, 2001, Table 1
    Cm=(1*ufarad*cm**-2)*area
    gl=(2.05e-5*siemens*cm**-2)*area
    El=-70.3*mV
    EK=-90*mV
    ENa=50*mV
```

```
g_na=(0.056*siemens*cm**-2)*area
g_kd=(0.006*siemens*cm**-2)*area
VT=-56.2*mV
# Reversal potentials
Ee=0*mV
Ei=-75*mV
# The model
eqs=Equations('''
dv/dt = (gl*(El-v)+ge*(Ee-v)+gi*(Ei-v)-g_na*(m*m*m)*h*(v-ENa)-g_kd*(n*n*n*n)*(v-EK))/Cm : volt
du/dt = (gl*(El-u)+ge*(Ee-u)+gi*(Ei-u))/Cm : volt
dm/dt = alpham*(1-m)-betam*m : 1
dn/dt = alphan*(1-n)-betan*n : 1
dh/dt = alphah*(1-h)-betah*h : 1

alpham = 0.32*(mV**-1)*(13*mV-v+VT)/(exp((13*mV-v+VT)/(4*mV))-1.)/ms : Hz
betam = 0.28*(mV**-1)*(v-VT-40*mV)/(exp((v-VT-40*mV)/(5*mV))-1)/ms : Hz
alphah = 0.128*exp((17*mV-v+VT)/(18*mV))/ms : Hz
betah = 4./(1+exp((40*mV-v+VT)/(5*mV)))/ms : Hz

alphan = 0.032*(mV**-1)*(15*mV-v+VT)/(exp((15*mV-v+VT)/(5*mV))-1.)/ms : Hz
betan = .5*exp((10*mV-v+VT)/(40*mV))/ms : Hz
''')
eqs+=OrnsteinUhlenbeck('ge',mu=geave,sigma=gestd,tau=5*ms)
eqs+=OrnsteinUhlenbeck('gi',mu=giave,sigma=gistd,tau=5*ms)
P=NeuronGroup(1,model=eqs,
threshold=EmpiricalThreshold(threshold=0*mV,refractory=3*ms),
implicit=True,freeze=True)

# Initialization
P.v=-70*mV
P.u=-70*mV
P.ge=0*nS
P.gi=0*nS

# Record traces
M = SpikeMonitor(P)
Mv = StateMonitor(P, 'v', record=[0])
Mu = StateMonitor(P, 'u', record=[0])
Mge = StateMonitor(P, 'ge', record=[0])
Mgi = StateMonitor(P, 'gi', record=[0])

run(10000*msecond)
subplot(311)
plot(Mge.times/ms,Mge[0]/siemens)
subplot(312)
plot(Mgi.times/ms,Mgi[0]/siemens)
subplot(313)
plot(Mv.times/ms,Mv[0]/mV)
plot(Mu.times/ms,Mu[0]/mV)
#show()

# Save network neurons & readout neurons
import scipy.io as sio
```

```
filename="VmDistModel3HH%d_Data" %(filenumber)

sio.savemat(filename,{'M':M.spikes,'Mtime':Mv.times,'Mv':Mv.values,'Mu':Mu.values,'Mge':Mge.values,'Mgi':gi.
values,'gl':gl,'geave':geave,'giave':giave,'gestd':gestd,'gistd':gistd})

return
```

4. Membrane conductance during blank and visual stimulation trials

Visually-evoked depolarization may result from increased membrane conductance due to opening of channels with depolarized reversal potentials, or from decreased membrane conductance due to closing of channels with hyperpolarized reversal potentials. In this section we provide evidence consistent with visually-evoked depolarization being accompanied by increased membrane conductance, as it is in primary visual cortex of anesthetized animals[24,25].

We estimated membrane conductance from voltage responses to hyperpolarizing current pulses of constant amplitude, and a fit of a sum of two exponentials to the voltage response[26]:

$$V(t) = I_{inj}\left[R_M\left(1 - e^{-\frac{t}{\tau_M}}\right) + R_E\left(1 - e^{-\frac{t}{\tau_E}}\right)\right] ,$$

where V is the voltage response, t is time, I_{inj} is injected current, R_M is membrane resistance, τ_M is membrane time constant, R_E is electrode resistance, and τ_E is electrode time constant. Membrane conductance is $1/R_M$.

During blank trials, membrane resistance estimates ranged from 60 MΩ to 280 MΩ, with a median of 142 MΩ (14 neurons, Extended Data Fig. 5a, left); the corresponding membrane conductance estimates ranged from 4 nS to 16 nS, with a median of 7 nS (14 neurons, Extended Data Fig. 5a, right).

In 2 neurons (Extended Data Fig. 5b, c; each row shows a different neuron), we estimated membrane conductance with hyperpolarizing current pulses during blank as well as visual stimulation trials. During blank trials (Extended Data Fig. 5b, c, left), current pulses elicited hyperpolarizations whose amplitude remained approximately constant throughout the trial, indicating that membrane conductance was approximately constant during blank trials. During visual stimulation trials in which preferred (Extended Data Fig. 5b, c, centre) or 45° from preferred (Extended Data Fig. 5b, c, right) orientations were shown, hyperpolarizations elicited by current pulses between fixation onset and stimulus onset had approximately the same amplitude as during blank trials (Extended Data Fig. 5b, c, left), indicating that pre-stimulus membrane conductance was similar to that during blank trials. After the onset of preferred (Extended Data Fig. 5b, c, centre) or 45° from preferred (Extended Data Fig. 5b, c, right) orientations, the hyperpolarizations elicited by current pulses decreased in amplitude,

indicating that membrane conductance increased during visual stimulation. These data suggest that the visually-evoked depolarizations we observed in primary visual cortex neurons of behaving primates are accompanied by increased membrane conductance, as it is in primary visual cortex neurons of anesthetized animals[24,25].

5. Spectral analysis of Vm and LFP

We computed power spectra for raw Vm, and Vm and LFP fluctuations from the trial average (i.e., residuals). Across the population of recorded neurons, the power of Vm and LFP fluctuations from the trial average declined approximately monotonically with frequency during blank trials, as well as during visual stimulation (Extended Data Fig. 6a). The approximately monotonic decay of Vm and LFP power with frequency during blank trials (Extended Data Fig. 6a, left panels) is consistent with previous studies of V1 of alert, behaving macaques[27,28]. Averaged across the population of recorded neurons, the ratio of Vm power at the preferred orientation to Vm power during blank trials showed a clear peak at 4 Hz (Extended Data Fig. 6b, top), which was the temporal frequency of the drifting sinusoidal grating visual stimulus. The power spectra ratio of Vm fluctuations from the trial average did not exhibit a peak at 4 Hz (Extended Data Fig. 6b, middle), suggesting that the temporal frequency of the stimulus is linearly reflected mainly in the trial-averaged response. The power spectra ratio of Vm fluctuations from the trial average was near unity at low frequencies and increased monotonically with frequency (Extended Data Fig. 6b, middle). The power spectra ratio of LFP fluctuations from the trial average was similarly near unity at low frequencies and greater at high frequencies, but showed a dip near 30 Hz[28] (Extended Data Fig. 6b, bottom).

We computed the magnitude of the coherence between Vm fluctuations from the trial average and LFP fluctuations from the trial average. There was markedly more coherence at low frequencies (0.5 - 4 Hz) than at high frequencies (30-50 Hz) during blank trials, than at the preferred orientation (Extended Data Fig. 7).

6. Supplementary discussion of spontaneous correlations

Our data show that spontaneous cortical activity in V1 of the alert fixating primate is not in an asynchronous high conductance state in which neurons receive nearly Gaussian aggregate input and Vm hovers below spike threshold. Instead Vm lies far from threshold, and exhibits occasional large fluctuations, and is correlated with the LFP. Our results differ with some recordings in awake animals obtained with sharp intracellular recordings[29,30], and are similar to some results in awake animals obtained with whole-cell intracellular recordings[31,32]. Here we discuss possible reasons for these differences.

Given that these differences seem to be correlated with the use of sharp or whole-cell intracellular recording methods, one may ask whether either or both of these methods are giving artifactual results. This is probably not the case, as similar in vivo results have been

obtained using both methods. For example, independent observations of up-and-down spontaneous Vm fluctuations in cortical neurons were first reported using whole cell[33] and sharp recordings[34]. The functional properties of V1 neurons measured by sharp recordings[35,36] and whole cell recordings[24,25,37-40] are largely consonant. Similarly, studies using in vivo sharp and whole-cell recordings yield a consistent picture of tone-evoked excitation and inhibition in the primary auditory cortex[41-49].

One potential explanation are differences in cortical area examined. For example, even under the same anesthetic state, primary auditory and dorsal posterior areas in the mouse auditory cortex[50] are characterized by differences in the periodicity of their spontaneous activity. In addition, while up and down states are commonly observed in many cortical regions in anesthetized animals[34], including V1[51], they are noticeably absent or diminished in the ketamine-anesthetized rat and cat AI[32,52,53]. In conjunction with these electrophysiological measurements, fMRI has revealed connectivity patterns that are divergent between cortical areas, and result in different patterns of resting state activity[54,55].

In addition, the difference between our results and the studies of Steriade, Timofeev and Grenier[29] may be due to a combination of a difference in behavioural state and cortical region. Our study examined V1 in alert, behaving primates, while Steriade, Timofeev and Grenier[29] studied cat pericruciate (motor) and anterior suprasylvian (association) gyri, or coronal (primary somatosensory) and posterior suprasylvian (visual association) areas during quiet wakefulness. Similarly, the study by Matsumura, Chen, Sawaguchi, Kubota and Fetz[30] measured membrane potential in the motor cortex of alert, behaving primates performing a motor response with the contralateral hand during a visual reaction-time task or an isometric wrist flexion–extension task. The dependence of correlations on behavioural state is supported by extracellular studies in alert, behaving primate motor cortex which indicate positive or near-zero average correlations depending on stimulus condition and task[56].

In contrast to the studies from motor cortex, extracellular studies in alert, behaving primates in the visual pathway have reported correlations during the pre-stimulus period[57-59]. These extracellular records are consistent the correlations we have observed in V1.

7. Vm-LFP correlations for flashed stimuli

To investigate whether our primary results hold for visual stimuli other than drifting sinusoidal gratings and under different task requirements, we also performed experiments in one monkey in which flashed Gabor stimuli (instead of drifting sinusoidal gratings) were presented, and in which the monkey had to saccade to the flashed Gabor stimulus (instead of maintaining fixation) in order to receive a reward (Extended Data Fig. 8a). The flashed Gabor duration was variable, as it was removed once the monkey initiated the saccade toward the target, but had a mean duration of 120 ms. Accordingly, whereas the drifting sinusoidal grating was dominated by a 4 Hz temporal frequency, the flashed Gabor stimuli had a broader range of temporal frequencies, and were more naturalistic in this particular respect.

As with the simple fixation task described in the main text, in this task requiring fixation followed by a saccade, there were nearly simultaneous Vm depolarizations and LFP deflections in the spontaneous activity during the pre-stimulus fixation period (Extended Data Fig. 8b, events marked by asterisks). We compared correlations between Vm and LFP fluctuations from the trial average during the pre-stimulus fixation period (Extended Data Fig. 8b, 1000 ms before and up to the red line indicating stimulus onset), with the correlations during the flashed Gabor stimulus (Extended Data Fig. 8b, period indicated by grey shading; 40 to 110 ms following the flashed Gabor. We included up to 30 ms after saccade onset in this period, because the visual latency for spike responses in the lateral geniculate nucleus is greater than 30 ms). Across the population, median Vm-LFP correlations were greater in magnitude during the pre-stimulus fixation period than during the flashed Gabor stimulus (Wilcoxon sign rank test, $p<0.05$), and median Vm-LFP correlations were not different from zero during the flashed Gabor stimulus (Wilcoxon sign rank test, $p=0.55$).

These data suggest that stimulus-evoked asynchrony in V1 occurs for visual stimuli other than drifting sinusoidal gratings and under different task requirements. The robustness of stimulus-evoked asynchrony in V1 of the alert, behaving primate is consistent with stimulus-evoked asynchrony with a variety of visual stimuli and task requirements in extrastriate visual cortex[57-59]. However, it is likely that there are stimuli with which stimulus-evoked asynchrony does not occur[11,60], and the limits of stimulus-evoked asynchrony remain to be determined.

In addition, these data suggest that the synchronized cortical state in the absence of visual stimulation is not restricted to monkeys that are performing a fixation task, but also occur when the animal is engaged in an active saccade task. This issue is further discussed in the following section.

8. Post-fixation saccade characteristics

A potential concern regarding our finding that in the absence of visual stimulation V1 is in a synchronized state is that our monkeys may have been drowsy due to the nature of the fixation task. This seems unlikely since, as discussed above, we observe similar results in one monkey engaged in a saccade task. In addition, to demonstrate that during our main experiment the monkeys were in an alert state, we analyzed their eye movement during the inter-trial-interval. If the monkeys were drowsy, we would expect the first inter-trial saccade to be slow and have a long latency following the removal of the fixation target. On the other hand, if the monkey is actively maintaining fixation during the trial, we would expect a saccade to occur shortly after the fixation point is terminated at the end of the trial. The analysis below shows that the monkeys tended to make rapid saccades (see also Supplementary Video), indicating that they were alert and actively engaged in the fixation task. In each of 2 monkeys (Extended Data Fig. 9a, b, monkeys W and T, respectively), the median latency of the first saccade after the post-fixation period was 217 ms and 314 ms (Extended Data Fig. 9, top), while the median peak velocity was 292 deg/s and 219 deg/s (Extended Data Fig. 9, top). These median latencies were

comparable to the range of latencies generally reported for visually cued saccades[61-64]; the median peak velocities were comparable to the 200-800 deg/sec range of peak velocities generally reported for visually cued saccades[61-63,65]. Note that monkey T sometimes decided not to move his eyes between trials, instead waiting until the next trial began. This is likely to reflect the fact that the minimal inter-trial interval was shorter for this monkey, and therefore, the monkey could increase its rate of reward by maintaining gaze close to the center of the screen in the inter-trial interval.

9. Intrinsic properties of recorded neurons

We examined the intrinsic properties in a subset of the recorded neurons by injecting current steps (Extended Data Fig. 10a). In all the neurons examined, the inter-spike interval increased with each successive spike evoked by the current step (Extended Data Fig. 10b), consistent with these neurons being regular spiking neurons[66] (i.e., pyramidal).

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