Attractor competition enriches cortical dynamics during awakening from anesthesia

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SUMMARY

Slow oscillations ($\lesssim 1$ Hz), a hallmark of slow-wave sleep and deep anesthesia across species, arise from spatiotemporal patterns of activity whose complexity increases as wakefulness is approached and cognitive functions emerge. The arousal process constitutes an open window to the unknown mechanisms underlying the emergence of such dynamical richness in awake cortical networks. Here, we investigate the changes in the network dynamics as anesthesia fades out in the rat visual cortex. Starting from deep anesthesia, slow oscillations gradually increase their frequency eventually expressing maximum regularity. This stage is followed by the abrupt onset of an infra-slow (~ 0.2 Hz) alternation between sleep-like oscillations and activated states. A population rate model reproduces this transition driven by an increased excitability that brings it to periodically cross a critical point. Based on our model, dynamical richness emerges as a competition between two metastable attractor states, a conclusion strongly supported by the data.

Keywords: Attractor dynamics, sleep-wake transition, neuronal oscillations, infra-slow oscillations

Introduction

While asleep or under anesthesia, the brain generates slow oscillations (SO), a pattern of activity that alternates between periods of activity or Up states, and periods of silence or Down states (Steriade et al., 1993; Sanchez-Vives et al., 2017). SO constitute a multiscale phenomenon in the brain, originating locally at the single-column level and propagating as traveling waves across the cortical surface (Massimini et al., 2004; Mohajerani et al., 2010; Huang, 2010; Stroh et al., 2013), while recruiting the cortico-thalamo-cortical loop and other subcortical brain structures (Wolansky et al., 2006; David et al., 2013; Sheroziya and Timofeev, 2014; Amigó et al., 2015). Such a global and stereotyped activity emerges from the synchronized cooperation between cortical assemblies oscillating between Up and Down states (Bazhenov et al., 2002; Compte et al., 2003; Destexhe, 2009). Under these conditions brain activity displays a relatively low degree of complexity in dynamical terms (Casali et al., 2013; Casarotto et al., 2016). Such low complexity at the mesoscale of local neuronal assemblies could be the result of the interplay between recurrent synaptic excitation and an activity-dependent adaptation or self-inhibition, giving rise to nonlinear dynamics that lead such networks to behave like relaxation oscillators (Compte et al., 2003; Gigante et al., 2007; Curto et al., 2009; Mattia and Sanchez-Vives, 2012; Levenstein et al., 2019).

The transition from the sleep to the awake state is known to bring the brain into a dynamical regime in which an enriched repertoire of activity is displayed with a higher degree of complexity (Casali et al., 2013; Schartner et al., 2017) often associated with desynchronized firing in time and space (van Vreeswijk and Sompolinsky, 1996; Destexhe, 2009; Renart et al., 2010). This dynamical richness allows the brain to perform state-dependent computations while maintaining sensitivity both to sensory inputs and to a wide repertoire of inner mental states (Buonomano and Maass, 2009; Deco et al., 2013). Complexity in the cortical network can emerge as an increasing influence of long-range functional connectivity *versus* local connectivity (Alkire et al., 2008; Bettinardi et al., 2015) leading to restless collective dynamics whenever a critical point of the phase diagram is approached (Beggs, 2008; Deco et al., 2013; Tognoli and Kelso, 2014). Changes in local nonlinear dynamics of neuronal assemblies are also thought to play an important role in this brain state transition (Bazhenov et al., 2002; Hill and Tononi, 2005; Curto et al., 2009). Indeed, the onset of input-output nonlinear responses can be naturally expressed by the same local assemblies oscillating during slow-wave activity (Curto et al., 2009; Mattia and Sanchez-Vives, 2012; Jercog et al., 2017), giving rise to "flip-flop" units displaying a state-dependent response to fluctuating synaptic inputs (McCormick, 2005; Linaro et al., 2011;

Mattia and Sanchez-Vives, 2019). Brain networks composed of such units can implement a wide range of computational capabilities ranging from enhancing or blocking sensorimotor processing, to integrating incoming information through long timescales (McCormick et al., 2015; Huang and Doiron, 2017). However, although the enhancement of the input-output nonlinear response is expected at the local assembly level (Mattia et al., 2013; Reig et al., 2015; Zerlaut and Destexhe, 2017), alternative interpretations of the experimental evidence about the synchronized-desynchronized state transition have been proposed. Indeed, the oscillatory behavior of local assemblies can also fade out due to a lowering of the excitability of the local networks, leading to a linearization of the input-output response (Curto et al., 2009). Due to these kinds of ambiguities, the mechanistic root of the transition from sleep or deep anesthesia to wakefulness is still far from being fully understood.

Synchronized-desynchronized state transitions thus provide a unique window into the potential diversity of the dynamical regimes that local cortical assemblies can express both autonomously and in response to changing input from the global network at the macroscale. Here, we exploit this opportunity by focusing on the dynamics underpinning the synchronized-desynchronized state transition at the local level of layer 5 (L5) neuronal assemblies, ant we aim to clarify the scenarios mentioned previously regarding an increase or decrease of the network excitability. For this purpose, we recorded the neuronal activity in L5 from the primary visual cortex (V1) of rats during the transition from deep to light anesthesia; that is, from the slow oscillatory activity towards a pattern of activity characterized by the periodic appearance of micro-arousal (MA) periods. The changes in the observed neuronal activity are fully captured by a population rate model in which SO spontaneously emerge from the interplay between recurrent synaptic excitation and activity-dependent self-inhibition (Compte et al., 2003; Mattia and Sanchez-Vives, 2012; Levenstein et al., 2019). As a result, L5 assemblies increase their excitability as the awake state is approached, eventually crossing back and forth a critical point displaying autonomously all the available dynamical regimes – a local enrichment likely contributing to the rise of complexity in the brain network at the macroscale.

Results

In order to study the transition across different levels of vigilance in the cortex, five rats were deeply anesthetized and the local field potential (LFP) of a neuronal assembly of L5 in V1 was continuously recorded while the anesthesia level progressively decreased (Fig. 1A). During the recovery from deep anesthesia, cortical rhythms underwent some gradual changes and eventually some abrupt ones, and this progressive transition was observed as different oscillatory patterns at the level of the LFP signal (Fig. 1B).

During deep anesthesia L5 neurons showed SO at a frequency of 1.17 ± 0.21 Hz (mean $\pm$ standard deviation (SD), $n = 5$ rats) (Steriade et al., 1993; Chauvette et al., 2011; Ruiz-Mejias et al., 2011). SO gradually became faster and more regular as the anesthesia level decreased (Fig. 1B). However, while reaching lighter levels of anesthesia, there was a characteristic abrupt onset of a new oscillatory pattern, in which the cortical SO was periodically interrupted by periods of low LFP amplitude: the MA states (Bergmann et al., 1987; Watson et al., 2016). The duration of these MA periods ranged from 0.68 ± 0.41 s to 10.67 ± 5.87 s (mean $\pm$ SD across $n = 5$ rats).

Gradual and abrupt changes in the oscillatory patterns when anesthesia fades

In order to quantify the changes occurring during the recovery from anesthesia, we computed the power spectral density (PSD) of the LFP in 1-min windows throughout the time course of the experiment. As shown in the spectrogram of a representative recording in Fig. 1C, during deep stages of anesthesia the dominant frequency was around 1 Hz and as the anesthesia level decreased, the frequency of the SO gradually increased, as shown by the monotonic increase of the median PSD (Fig. 1C). To perform population analyses across the subjects, we singled out four intervals of 10 min corresponding to different levels of anesthesia progressively advancing from deeper to lighter: Deep1 (D1), Deep2 (D2), Light1 (L1) and Light2 (L2) (Fig. 1A). During the deeper phases of anesthesia (D1 and D2), the median PSD frequency increased from 1.17 ± 0.21 Hz to 1.21 ± 0.19 Hz (mean $\pm$ SD); and continued increasing during the lightest phases (L1 and L2) from 1.40 ± 0.24 Hz to 1.66 ± 0.42 Hz (Fig. 1F-left).

This increase in the frequency of the SO was also observed as a shift in the peak at slow frequencies of the PSD of the D1 and D2 intervals (Fig. 1D). At the same time, the spectrogram showed that the range of frequencies at which the recorded local network oscillated shrank as the anesthesia level decreased (the red and yellow areas around 1 Hz in Fig. 1C became concentrated in a smaller frequency range from D1 to D2). We quantified the reduction of the range of frequencies visited by the cortical network using the interquartile range (IQR, a measure of the variability of a distribution) which is the difference between the frequencies at the $75th$ and $25th$ percentiles of the PSD distribution computed at each minute during the course of the experiment. We found that, at population level, the range of frequencies started at 0.88 ± 0.07 Hz in D1 and dropped to a minimum in D2 with a range of 0.51 ± 0.28 Hz on average (Fig. 1F-right).

These results suggest that during the first part of the transition from deep to light anesthesia (from D1 to D2) the SO not only became faster but also more regular, since the IQR, representing the range of the frequencies visited around this median value, was reduced. This increased regularity of SO is highly suggestive of an optimal level of excitability to express this rhythm, as reported *in vitro* (Sancristóbal et al., 2016). When continuing towards lighter anesthesia (L1 to L2), the ongoing increase in regularity was disrupted by the sudden

appearance of MA states, which were identified as periods of low LFP amplitude interrupting the SO every 5 s (0.2 Hz) and therefore associated with a peak in the low-frequency range of the spectrogram (Fig. 1C) and the PSD (Fig. 1D)

The fact that another frequency in the lower region of the spectrogram became relevant would explain the larger IQR observed at the population level during the last phase of the transition: IQR increased up to 0.89 ± 0.33 Hz in L1 and to 1.49 ± 0.45 Hz in L2 (Fig. 1F). Similarly, the power of the infra-slow oscillations ($0.01 - 0.5$ Hz) increased since the first appearance of MA until the end of the experiment ($p = 0.045$, *two-sample t-test*, Fig. 1G).

In order to investigate the nature of these periods of sustained asynchronous activity, we inspected the high-frequency content of the LFP signal recorded during different levels of anesthesia. We found that the power of beta and gamma bands (intervals $15 - 30$ Hz and $30 - 100$ Hz, respectively) progressively increased during the transition from deep to light anesthesia, in particular during L1 and L2 (Fig. 1E,G). Beta power in L2 was significantly higher than in D1 ($p = 0.045$, *two-sample t-test*). Gamma power in L1 had already increased significantly from D1 values and continued increasing during L2 ($p = 0.033$ and $p = 0.027$, respectively, *two-sample t-test*). These results are in accordance with the increased high-frequency content observed in the EEG of the awake cat compared to the sleep state (Destexhe et al., 1999).

Appearance of a new activated state

To describe the temporal patterns observed in the LFP during the fading of anesthesia, we extracted the multi-unit activity (MUA) signal from the raw signal, and singled out Up and Down states by thresholding the log(MUA) values (Ruiz-Mejias et al., 2011) (Fig. S1A). We detected the Down-to-Up state transitions occurring during 10-min intervals corresponding to different levels of decreasing anesthesia (D1, D2, L1 and L2, respectively). We then produced a raster of the MUA values during the Down-to-Up state transitions detected at each interval (Fig. S1B).

Sorting the Down-to-Up state transitions by Up state duration, we observed some interesting features concerning a new type of activity pattern. As mentioned above, an activated state with longer duration than Up states appeared during the lightest phases of anesthesia: the MA. To differentiate Up states from MA, which shared higher levels of MUA than Down states, we used a threshold on the moving variance of the LFP signal, since the LFP during MA showed very low variance compared to periods of SO (Fig. S1A). We then computed the mean duration of Up, Down and MA states in 1-min windows across the experiment. While the Up state duration remained almost constant with a small tendency to increase, the Down state duration decreased monotonically, at some point converging to duration values very similar to those of the Up state, resulting in an increase in frequency and regularity of the SO (Fig. 2A).

The population level analysis showed that Down states decreased monotonically from deep to light anesthesia, thus increasing the SO frequency, Up states remained rather constant even when they elongated slightly during the initial part of the transition, and MA progressively elongated, resulting in a positive correlation between MA duration and its onset time (Fig. 2B). This evidence was compatible with the scenario in which the increasing amount of time spent by the L5 network in the MA state led to a decrease in periods spent displaying coherent SO with increasing frequency.

Optimal anesthesia level regularizing SO

As mentioned above, the reduction of the anesthesia level from D1 to D2 led to a more regular pattern of SO. However, at lighter levels of anesthesia, MA states altered the oscillatory pattern and thus weakened its regularity. To further investigate these changes, we computed the auto-correlogram of the MUA signal in 1-min time windows. We found that when the anesthesia level decreased, the time lag at which we found peaks of correlation decreased (Fig. 3A), indicating that the firing of the local network became more coherent as the anesthesia level decreased from D1 to D2. Simultaneously, a minimum in the coefficient of variation (c_v) of both Up and Down state duration was reached (Fig. 3B).

Up state duration showed a bimodal distribution during deep anesthesia, with peaks at short (110 ms) and long (330 ms) durations (Fig. 3C,D). Interestingly, the fading of anesthesia occurring from D1 to D2 periods shrank the distribution of Up state duration. Indeed, right before the appearance of the first MA the distribution of Up state duration became unimodal (with a preferred Up state duration slightly longer; 380 ms). On the contrary, when MA states started to appear (L1 to L2), the Up state duration distribution became bimodal again, breaking the MUA coherence and producing a decrease in regularity of the Up state duration.

From the perspective of the dynamical system theory, such maximization of the regularity of SO, and thus the onset of more stereotyped Up states, is suggestive of an intriguing hypothesis: at this stage of the transition towards wakefulness (D2 period), our system seems to pass through a region of its parameter space where only a dynamical state is available – a limit cycle – while at deeper and lighter anesthesia levels other attractor states are available to be visited. Consequently, the wandering across these attractors can account for the observed changes in the variability of Up and Down state duration.

MA states are not longer Up states

It seems a logical question to wonder whether MA states are just longer Up states. We investigated thoroughly this question, starting by evaluating the FR and the duration of both states during the lighter phases of anesthesia (Fig. S3). To determine the level of MUA of MA states and compare it with that of the Up states, the asymptotic FR of Up and MA states was computed in 1-min time windows (Fig. 4A). While the asymptotic FR of Up states showed a tendency to increase as the anesthesia faded from L1 to L2, that of MA remained almost constant. Although those tendencies were

not significant at the population level (Fig. 4B), we observed in all cases that the mean asymptotic FR of MA occurring during the period from L1 to L2 was significantly lower than that of the Up states occurring during the same period (Fig. 4C). This was already observed in the raster plots of the MUA around the transition towards the Up state or towards a MA state in the L1 and L2 intervals (Fig. S1B).

As both state duration and activity level of MA and Up states are different, one reasonable hypothesis is that their mechanistic, dynamical basis has different origins. In the following section we investigate this issue and use a model network of the L5 cell assembly to provide a coherent dynamical picture of the transition from deep to light anesthesia.

State alternation onset in a model of the fade out from anesthesia

Data analysis seemed to indicate that during the late phases of the recovery from anesthesia there was a competition between two types of dynamical regimes: the oscillatory (the slow Up/Down state alternation) and the activated (MA states).

In order to investigate the mechanistic root of these dynamics, we developed a population rate model capable of reproducing the features of the lumped activity of the L5 assemblies we observed experimentally (Fig. 5A). The aim of the model was to represent a network of a finite number of neurons displaying two metastable activity states at high (Up) and low (Down) FR $\nu(t)$ due to a sufficiently strong recurrent synaptic excitation and a sigmoidal input-output gain function $\Phi(I)$, giving the asymptotic ν of a neuron receiving a current I. A quasi-regular alternation between Up and Down states was ensured by the presence of an activity-dependent adaptation level $a(t)$ providing a proportional self-inhibitory current with strength g_a (Mattia and Sanchez-Vives, 2012).

In addition, the activity $\nu(t)$ of the network was modulated by an external input current I_{ext} representing the net excitatory input due to the presynaptic activity coming from neurons external from the modeled network, and additionally by an oscillatory (sinusoidal) external input ($I_{\sin}$) that under suitable dynamical conditions could be turned on to reproduce the SO-MA alternation observed under light anesthesia (L1-L2).

To include the endogenous fluctuations of $\nu(t)$ due to the unavoidable statistical variability of the spikes emitted per unit time in a network composed of a finite number of neurons (Mattia and Del Giudice, 2002), we also added white noise to the input current I with appropriate intensity.

The state of this two-dimensional system is a point in the phase plane (a, ν) which moves in time forming specific trajectories. Due to the nonlinearity in amplifying input current I and the inhibitory feedback $-g_a\, a$ underlying spike-frequency adaptation, this kind of system can display a rich repertoire of dynamical regimes (Strogatz, 2014). Indeed, by inspecting the bifurcation plane defined by the adaptation strength g_a and the excitability level associated with the current I_{ext}, regions with both attracting fixed (equilibrium) points and with periodic orbits (limit cycles) can be identified (Fig. 5B) (Mattia and Sanchez-Vives, 2012; Levenstein et al., 2019). More specifically, when the inhibitory g_a or the excitatory I_{ext} component is predominant, a stable fixed point (attractor) arises at relatively low (LAS, or low attractor state, top-left corner) or high (HAS, high attractor state, bottom-right corner) FR, respectively. When self-inhibition is sufficiently balanced by the network excitability, an unstable fixed point emerges giving rise to an oscillatory regime (SO region), related to a limit cycle.

To mimic the fading out of anesthesia, we implemented a rather specific increase of the excitability degree in the model by simultaneously increasing the external current I_{ext} and reducing the strength of adaptation g_a. We took into account that ketamine is an NMDA receptor antagonist and as such reduces the glutamatergic synaptic input from upstream cortical and subcortical areas (Alkire et al., 2008; Brown et al., 2011). This, together with a reduced excitatory noradrenergic input to infragranular layers expected when the locus coeruleus (McCormick, 1992) is inhibited by medetomidine (Brown et al., 2011), led us to impose a low initial value for I_{ext}, eventually increasing it as the anesthesia fades out. As in the work of Hill and Tononi (2005) and Destexhe (2009), the reduction of the adaptation-related feedback g_a was implemented to mimic the effect of increasing acetylcholine (ACh) levels associated with the ketamine anesthesia wearing off (Pal et al., 2015). Indeed, higher levels of ACh lead to a larger blockage of the slow Ca^{2+}-activated K^+ current (McCormick, 1992), reducing the spike-frequency adaptation of pyramidal neurons and eventually contributing to the increase in cortical excitability as anesthesia fades.

As a result, the gradual changes of g_a and I_{ext} are shown in Fig. 5B as a gray-dashed trajectory moving from the deepest anesthesia level D1 to the lightest L2 we singled out in the experiments. Moving the system along this trajectory, all the dynamical conditions observed in the different stages of anesthesia were reproduced: irregular SO in D1, regular SO in D2 and the SO-MA alternation in L1-L2 (periodically crossing the edge between SO and HAS, Fig. 5B). Interestingly, across this SO-HAS boundary the model predicted a specific kind of transition, namely a subcritical Hopf bifurcation, characterized by the coexistence of a limit cycle (SO) and an equilibrium point (HAS). As discussed later, this characteristic feature turned out to be decisive in reproducing the changes of the MUA observed under light anesthesia.

In order to visualize how the different dynamical regimes were generated by this simple bidimensional system, we plotted the nullclines of $\nu(t)$ and $a(t)$ (Fig. 5C) for different levels of anesthesia (D1, D2 and L2). Nullclines indicate where the time derivatives of the variables vanish ($\dot{\nu} = 0$ and $\dot{a} = 0$, respectively). The crossings of the nullclines, the fixed points, are the points in the parameter space where both derivatives are zero. During D1, the Down state was a stable fixed point and the irregular occurrence of Up states was due to the aforementioned endogenous fluctuations (Fig. 5D-top). In D2 (Fig. 5C-center), the unstable fixed point indicated the pres-

ence of a limit cycle that led to regular oscillations as in the experimental data (Fig. 1B, second row). When the oscillatory external input ($I_{\sin}$) was turned on (during L1-L2), the position of the ν-nullcline changed over time. An increase (decrease) in $I_{\sin}$ shifted the nullcline towards the left (right) in the (a,ν) plane, producing the dashed (solid) black curves in Fig. 5C-bottom). For minimal values of $I_{\sin}$, an unstable fixed point (limit cycle) produced a periodic orbit around the crossings of the ν- and the a-nullcline giving rise to the oscillatory regime. For maximal values of $I_{\sin}$, a stable fixed point was created at the crossing between the two nullclines at a high value of ν, leading to a HAS regime. Thus, during the latter phases of the transition from deep to light anesthesia, the presence of $I_{\sin}$ induced a periodic subcritical Hopf transition between the limit cycle (SO region) and the high activity attractor (HAS region), resembling the SO-MA alternation observed in the experiments (Fig. 5D-bottom).

The synthetic MUA obtained in the simulation displays a time course of its Fourier-frequency content which is remarkably similar to that recorded during the experiments (compare Fig. 1C and 5E), reproducing the increase in the frequency of the SO and the appearance of a peak in power at ~ 0.2 Hz. Moreover, the evolution of the duration of the Down, Up and MA states during the transition from deep to light anesthesia (Fig. 5F-top) was fully consistent with experimental observations: mean Down state duration decreased, mean Up state duration increased and mean MA duration increased from L1 to L2 periods. Finally, by comparing the MUA level of Up and MA states (during L1 and L2 light anesthesia periods), we found that MA had, on average, lower activity levels than the Up states (Fig. 5F-bottom) as seen in the experiments.

Footprints of the modulation of attractor stability in model

We further investigated the dynamics underlying the switch from the oscillatory to the activated state, that we identified by the Down-to-MA transition. We first analyzed the time course of the activity of the model network around the Down-to-Up and Down-to-MA transitions and found that the former had a larger MUA amplitude, involving a lower Down state MUA level with respect to the latter (Fig. 6A-top). Moreover, the transitions towards MA displayed a larger degree of variability when compared to the transitions towards Up states.

To explore whether the variability among MA could be generated by differences in pre-transition activity, Down-to-MA transitions were sorted by the level of activity in the previous Down state and grouped into two clusters of equal size (Fig. 6B-top). We found that the cluster characterized by a lower level of activity during the previous Down state reached higher values of activity during the beginning of the MA. In our model this was due to the slow oscillating input $I_{\sin}$ whose intensity at the time of the Down-to-MA transition determined the network FR ν (Fig. S2A). In the phase portrait (a,ν), this gave rise to different trajectories (Fig. S2B). Those starting with the lowest $I_{\sin}$, and hence with the lowest activity, closely resembled the limit cycle of the relaxation oscillation underlying the SO regime. In this case the attractive force towards the limit cycle is expected to be stronger than for larger $I_{\sin}$. As a result, the activity fluctuations in the forthcoming high-firing state are expected to be smaller as the not-yet-destabilized basin of attraction of the SO is still relatively narrow (Mattia and Sanchez-Vives, 2012; Mattia et al., 2021).

In order to quantify the destabilization of the limit cycle, we evaluated the size of such fluctuations at the beginning of the MA by computing the inter-state SD for each group of Down-to-MA transitions. We found an anti-correlation ($\rho_{pearson} = -0.92, P < 10^{-6}$) between the level of activity reached during the transition (initial peak) and the SD at the peak of the MA (Fig. 6C-top).

As previously discussed, the transition to the MA in the model is due to the creation of a stable fixed point (white diamond in Fig. 5C-bottom-left). Changes in time of $I_{\sin}$ are also expected to shape this attractor, determining the time course of the averaged profile of MUA during MA (Fig. 6B-top). Firstly, we observed that there was a strong effect of adaptation that reduced the FR after the initial peak of activity, similar to that seen during the offset of Up states (Sanchez-Vives and McCormick, 2000; Compte et al., 2003). However, the activity did not drop completely, but rather slowly increased again for a few hundred milliseconds (gray shaded intervals in Fig. 6B).

We evaluated the MUA mean and SD at consecutive time windows of 100 ms starting at 500 ms after the MA onset (gray shaded squares in Fig. 6B-top) finding that (Fig. 6D-top) they were strongly anti-correlated ($\rho_{pearson} = -0.95, P = 0.015$). This suggests that while the level of activity increased, the size of fluctuations decreased, reflecting the presence of a fixed point whose stability was progressively increased.

Evidence of attractor stability changes in experiments

Our model predicted the presence of more than one attractor whose stability would be modulated as anesthesia fades out by the oscillating external input, leading to the dynamics shown in Fig. 5. In addition, the shape of the related basin of attractions was state-dependent, changing the state stability and the activity fluctuations in a peculiar way. We tested these predictions in the experimental data by comparing the average profile of the normalized log(MUA) for the Down-to-Up state transition and the Down-to-MA transition. The profiles were centered around the transition time and averaged over the experiments(Fig. 6A-bottom). According to the prediction, the amplitude of the initial MUA peak was larger in the Down-to-Up state transition.

To investigate the sources of variability among Down-to-MA transitions, MA states were sorted by the level of activity in the previous Down state and grouped into two clusters of equal size, as in the simulated data. The within-cluster average profiles around the transition (Fig. 6B-bottom) confirmed that the cluster characterized by a lower MUA level during

the Down state before the transition had a higher peak in MUA during the MA. As for the model, we evaluated the SD of the MUA at the peak of activity during the MA in each cluster and found a significant anti-correlation ($\rho_{pearson} = -0.77, P = 0.024$) between mean and SD of the MUA across different clusters (Fig. 6C-bottom), enforcing the hypothesis of a progressive destabilization of the SO. We observed in all clusters that the initial drop of activity after the peak was followed by a slow increase in the MUA level during the late part of the MA (Fig. 6B-bottom). Confirming the model predictions, the increase in the mean MUA was accompanied by a decrease in the SD, showing a significant anti-correlation ($\rho_{pearson} = -0.85, P = 0.016$; Fig. 6D-bottom) supporting the hypothesis of a progressive stabilization of the MA attractor.

Our results indicate that the dynamics of the cortical assemblies during the recovery from deep anesthesia are governed by the competition of two attractor states, a limit cycle that leads to oscillatory activity and a stable fixed point at high values of FR that leads to asynchronous periods (MA), and that this competition is modulated by an external oscillatory input.

Brain networks can generate SO-MA oscillations

In order to reproduce the alternation between SO and MA our population rate model had to incorporate an exogenous sinusoidal input I_{sin} modulated at 0.2 Hz, causing the system to cross a critical point back and forth. Different brain circuits might in principle provide such input during the arousal process. The ascending reticular activating system (ARAS) in the brainstem is an ideal candidate, as it is causally involved in the regulation of sleep-wake transitions (Kandel et al., 2013). This hypothesis is partially supported by the evidence that separating the brain from the ARAS in ketamine anesthetized cats, the alternation between slow-delta oscillations and low voltage, fast wave activity (reminiscent of MA periods) is disrupted (Miyasaka and Domino, 1968): under this condition SO are no longer interrupted by awake-like activity periods. Similar observations were found in rats under urethane anesthesia (Clement et al., 2008; Chan et al., 2015). In this case an ultra-slow rhythmic alternation between "activated" (low-voltage, fast-activity) periods and "deactivated" SO phases were interrupted by the stimulation of a cholinergic nuclei of the ARAS, the pedunculopontine tegmental nucleus.

A question then arises: can the interplay between a cortical network and a subcortical node lead to the autonomous emergence of the SO-MA loop? To address this point we added explicitly a population rate model of the brainstem network in our theoretical representation of L5 networks, considering it as the source of an alternating input I_{BS} functionally equivalent to I_{sin} (Fig. 7). This input is provided by the brainstem activity ν_{BS}, which in turn integrates the cortical FR ν on a long timescale (tens of seconds, Fig. 7A) eventually giving rise to the SO-MA infra-slow rhythm. This integration acts as a low-pass filter of the cortical activity leading to a rising and a decaying phase of I_{BS} as the average FR during SO and MA periods is lower and higher, respectively (Fig. 7B). In this way, the fast dynamics of the L5 network are slowly modulated by the brainstem activity, drifting the system back and forth across a subcritical Hopf bifurcation where the cortical module is bistable; that is, the limit cycle of SO and the MA fixed point coexist as shown in Fig. 5. The bistability modulation is apparent in the hysteresis loop shown in Fig. 7B-C where for the same I_{BS} both SO and MA are expressed in complementary phases of the cycle. This slow-fast dynamics underlying the cyclic permanence and destabilization of both SO and MA is mathematically equivalent to the 'elliptic burst' displayed by other excitable systems at the single neuron level (Rinzel and Ermentrout, 1998). Taking into account the quasi-static modulation of the excitability level of the cortical module *via* the external drive I_{ext}, the distance from the critical point can be changed to tune the relative duration of SO and MA periods associated with different levels of anesthesia (Fig. 7B-C). As a result, in a suited three-dimensional subspace of states, a simple cortical-brainstem model can autonomously give rise to trajectories unfolding nested loops with widening size as anesthesia fades out (Fig. 7B,C-left): a dynamical organization which could be unfolded in experiments with cortical and subcortical simultaneous recordings.

Discussion

Our results indicate that the transition from deep anesthesia to wakefulness, far from being a continuum, is characterized by both gradual and abrupt changes in the LFP and MUA dynamics. This can be fully explained as a progressive imbalance between two competing attractor states. Crucially, we show that the transition from the oscillatory (i.e., slowly alternating metastable Up and Down states) to the asynchronous regime does not emerge as a progressive morphing of one state (the SO) into another (the MA state), but rather passes through a slow, periodic (~ 0.2 Hz) bouncing between SO and MA in which the latter occupies a progressively increasing fraction of the cycle, eventually surviving as the only available network state when wakefulness is approached (Fig. 2B). This scenario is qualitatively different from the one emerging in similar nonlinear systems aiming at modeling spontaneous brain activity which, in the absence of external inputs, restlessly move around a mean-field critical point, eventually giving rise to a scale-invariant distribution of the MA duration (Deco et al., 2013; di Santo et al., 2018). The SO-MA alternation is also not captured by cortical network models in which the population activity is represented by a single stochastic state-variable (Deco et al., 2009). Indeed, in these models Up and Down states are metastable attractors and during light anesthesia the network hops between them randomly in time, which is incompatible with the experimental coherence of the 0.2 Hz rhythm (Fig. 1C). Furthermore, in this framework Up states would resemble small fragments of wakefulness (Destexhe et al., 2007) as they represent a continuum with the activated MA state. In contrast, the results we report for cortical activity under different levels of anesthesia seem to

challenge this view, since Up and MA states show markedly different features both in terms of MUA profiles in time and in the intensity of the activity (Fig. 4, 6 and Fig. S3).

Before crossing the critical point separating the oscillatory and the asynchronous regimes, as the anesthesia fades out from the deepest level (D1), the SO become maximally frequent and regular as level D2 is approached (Fig. 1C,F; Fig. 3). This increase in frequency and regularity of the SO is consistent with previous findings indicating that, at the macroscale, coherence between distant cortical areas at the frequency of the SO increases as the anesthesia level decreases and that the peak of correlation shifts to slightly higher frequencies (Bettinardi et al., 2015). Here, the increasing frequency of SO is due to the monotonic decrease of the Down state duration, supporting the hypothesis of an increased excitability of L5 assemblies which results in a destabilization of the low-firing state (Fig. 2). As the Down state becomes less stable, SO reach their maximum regularity (minimum c_v of both Up and Down state duration, Fig. 3B) signalling the absence of other competing attractor states. The strong stability of SO at this anesthesia level has to be considered a non-physiological condition. Indeed, under natural sleep the variability of Up state duration is markedly larger (Watson et al., 2016), although under the deepest non-rapid eye movement (NREM) sleep stage regularity measured as the height of the 1 Hz peak in the EEG power spectrum is at a maximum (Amzica and Steriade, 1997; Borbély et al., 1981). However, the evidence of a strongly stable limit cycle would explain why the bimodal distribution of Up state duration becomes unimodal in the D2 stage (Fig. 3C-D). As this bimodality may be due to an inhibitory rebound from subcortical structures like the thalamus (Mattia et al., 2021), a stronger stability of SO would make them independent from this kind of exogenous input leading to more stereotyped Up states. In addition, as a result of such resilience to external perturbations we expect that a minimum of perturbational complexity (Casali et al., 2013) should be measured in the D2 stage.

The emergence of different dynamical regimes in the probed L5 assemblies was fully captured by a minimal population rate model. Under mean-field approximation, the model provides an effective description of a network of excitatory integrate-and-fire neurons with spike-frequency adaptation (Gigante et al., 2007). Under the reasonable hypothesis that synaptic inhibition is faster than the excitatory one, this mean-field description can be extended to accurately describe a network of slow excitatory and fast inhibitory neurons provided that an effective gain function $\Phi(I)$ is taken into account (Mascaro and Amit, 1999). This approach has been proven to be effective in working out the bifurcation diagram of realistic local networks like L5 assemblies (Mattia and Sanchez-Vives, 2012). However, some limitations of this modeling framework should be remarked upon. Firstly, high-frequency oscillatory components like those we found in the gamma band (Fig. 1E,G) cannot be reproduced due to the assumption of slow synaptic excitation. Secondly, L5 assemblies are not isolated networks and spatially extended connections with other layers and areas should be taken into account in order to capture the richness of slow-wave activity (Capone and Mattia, 2017; Capone et al., 2019) across brain states (Hill and Tononi, 2005; Krishnan et al., 2016; Dasilva et al., 2021).

In our population rate model, to mimic the transition from irregular SO (D1) to the onset of MA periods (L1-L2), we implemented a rather specific increase of the excitability degree by simultaneously increasing the external current I_{ext} and reducing the adaptation strength g_a. In this way, we modeled the effects of ketamine (an NMDA receptor antagonist) affecting the excitatory input I_{ext} from upstream cortical and subcortical areas (Alkire et al., 2008; Brown et al., 2011). The other anesthetic – medetomidine – is an $\alpha 2$ adrenergic receptors (AR) agonist leading to an effective inhibition of the neurons in the locus coeruleus. This major arousal nucleus delivers noradrenaline (NA) to the cortex and to sleep-promoting neurons in the pre-optic area of the hypothalamus (Akeju and Brown, 2017; Reimann and Niendorf, 2020). Less NA promotes sleep-like global brain states *via* inhibition of the brainstem which in turn hyperpolarize thalamo-cortical and cortical neurons. Hence, medetomidine can be effectively modeled as a bottom-up reduction of I_{ext} in cortical networks, which we added to the above top-down effect directly due to ketamine (Mashour and Hudetz, 2017). On the other hand, as in Hill and Tononi (2005) and Destexhe (2009), the lowering of the adaptation-related feedback g_a mimicked the effect of the increasing ACh levels induced by the wearing off of ketamine-anesthesia (Pal et al., 2015). This modeling scenario of arousal from anesthesia differs from the one proposed by (Bazhenov et al., 2002; Deco et al., 2014; Krishnan et al., 2016), where, in addition to an increased excitability of the cortical network due to decreased-leak K^+ currents (equivalent to an increase of I_{ext}), a reduction of pyramidal-to-pyramidal glutamatergic transmission is incorporated to reproduce the transition towards the awake-like asynchronous state, resulting in a linearization of the input-output response function (Curto et al., 2009). Alternatively, in our framework the same network arousal leads to a cortical network composed of L5 neuronal assemblies capable of expressing a state-dependent response function (like "flip-flop" units) which contribute to a further increase in the complexity of the collective dynamics of the awake-like (D'Andola et al., 2018; Dasilva et al., 2021) brain.

In our case the nonlinearity of the input-output gain function is required to reproduce the abrupt switch between the two phases of the SO-MA transition. We reproduced this experimental evidence by driving the model to cross these two regions of the bifurcation diagram through a subcritical Hopf bifurcation.

According to the hypothesis that MA and SO are two competing attractor states, the increased persistence in time of one of them is due to the destabilization of the other, and as a result, the orbit attracting the Up-Down state cycle loses its stability drifting towards the MA, with lower FR than the Up state (Fig. S2B).

The fingerprint of such attractor competition was then a mean-SD anticorrelation of the MUA that we remarkably found in the experiments (Fig. 6C,D), due to the widening of the FR fluctuations associated with a progressively weakened attracting force towards the SO orbit.

Our experimental data shows that SO and MA periods alternate at a stable frequency of 0.2 Hz. A similar phenomenon occurs in humans with ketamine at general anesthesia levels (Akeju et al., 2016; Li and Mashour, 2019) or cats under light ketamine anesthesia (Miyasaka and Domino, 1968; Mori et al., 1971). Intriguingly, modeling the wearing off of the medetomidine alone as a change of I_{ext} would lead to a horizontal trajectory in the plane (I_{ext}, g_a). As a result, the SO-HAS border would be crossed where only a supercritical Hopf bifurcation is expected; that is, where SO and MA do not coexist simultaneously, and hence without the possibility of engaging any competition. This would explain why 'gamma bursts", similar to those during light anesthesia (Fig. 1D,E), are not observed under anesthesia with α2AR agonists alone (Purdon et al., 2015). The periodic transition between SO and MA then appears to be a universal hallmark of the arousal process from the specific ketamine-induced anesthesia in mammals.

Considering the brainstem as the possible source of such periodic modulation of cortical excitability, it is tempting to interpret infra-slow oscillations ($0.02 - 0.2$ Hz), ubiquitously observed during natural sleep (Vanhatalo et al., 2004) or resting wakefulness (Raichle et al., 2001), as another expression of the cyclic bouncing between metastable SO and MA attractor states. A remarkable example is the cyclic alternating pattern (CAP), described as short and repetitive interruptions of the normal sleep oscillatory activity in humans (Terzano et al., 1985; Parrino et al., 2012). CAP periods range from 20 s to 40 s (Terzano and Parrino, 2000; Achermann and Borbely, 1997); that is, in a slower frequency band than the 0.2 Hz we report here. Notably, CAP has been proposed as a natural marker of sleep instability (Parrino et al., 2012), as it often onsets during the REM/NREM sleep transitions.

Indeed, administering an arousing stimulus during the activated states of CAP, SO are immediately elicited. Such susceptibility to external perturbations and the sensitivity to the arousal level are both dynamical features expressed by a cortical network working close to a critical point, as in the one presented here. Differences in the pace of the SO/MA alternation found between natural sleep and anesthesia might be explained by a different mechanistic origin of I_{sin}. However, a recent finding highlighted that NREM sleep periods can be further subdivided into two stages with the deepest one systematically displaying a prominent peak in the EEG power spectra in the $0.1 - 1$ Hz range (Onton et al., 2016), well compatible with the infra-slow rhythm we measured.

Despite the known differences between natural sleep and ketamine-induced anesthesia (Chauvette et al., 2011; Nghiem et al., 2020), all this body of evidence seems to support the hypothesis that the SO/MA alternation at around ~ 0.2 Hz is a universal infra-slow rhythm the brain spontaneously expresses whenever a specific critical point between the synchronized sleep-like and the desynchronized awake state is approached.

We believe that the theoretical and analysis framework we developed here could be an effective tool in identifying the possible common origin of the infra-slow oscillations found during the awakening from natural sleep and deep anesthesia.

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Author contributions

NTC, CC, MVSV and MM wrote the paper. NTC, MM and MVSV conceived the idea. NTC performed the experiments and analysis. MVSV supervised the experiments. CC and MM performed the models and analysis.

Declaration of interests

The authors declare no competing interests.

Figure titles and legends

Figure 1. Rhythms involved in the transition from deep anesthesia towards wakefulness. A. Sketch of the time events used to define the different stages (D1, D2, L1 and L2) of the transition towards wakefulness. Occurrence time of each event is averaged across animals ($n = 5$ rats) in the lower row. **B.** LFP traces extracted at each stage of the transition in a representative recording (color coded as in the sketch in A). Note that, when recorded in infragranular layers, the LFP shows an Up (Down) state as a negative (positive) deflection. **C.** LFP Spectrogram ($0.01 - 5$ Hz). Black superimposed trace corresponds to the median of the distribution of the PSD values at each time of the experiment. Blue, cyan, magenta and red vertical dashed lines indicate the boundaries taken in this example for each transition stage. Left: histogram of the spectrogram values throughout the experiment. **D.** and **E.** PSD ($0.01 - 5$ Hz and $5 - 200$ Hz respectively) of the LFP recorded at different stages of the transition towards wakefulness. Gray shaded areas indicate the frequency ranges used in G to compare the power at each frequency band in the different intervals. **F.** Population averages of the median PSD (left) and the IQR of the PSD (right) during each stage of the transition. **G.** Population averages of the power of different frequency bands during each stage of the transition. For panels F and G, black circles represent the mean of the distributions at each interval. On each box, the central line is the median ($50th$ percentile), the edges of the box are the $25th$ and $75th$ percentiles and the whiskers extend to the most extreme data points not considered outliers. $*p < 0.05$, $**p < 0.01$, two-sample t-test, $n = 5$.

Figure 2. Changes in Up, Down and MA state duration from deep anesthesia towards wakefulness. A. Up, Down and MA state duration computed in 1-min time windows across the experiment. **B** Population averages of Up and Down state duration in the different stages of the transition towards wakefulness (color coded as in the sketch in Fig. 1A). Right: correlation between the duration of the MA state and its onset time (in the normalized time from L1 to L2). Boxplots as in Fig. 1F,G.

Figure 3. Optimal anesthesia level regularizing slow oscillations A. Auto-correlogram of the log(MUA) signal computed at 1-min time windows across the experiment. Blue, cyan, magenta and red vertical dashed lines in A and C indicate the boundaries taken in this example for each transition stage. **B.** Mean coefficient of variation (c_v) of the duration of Up and Down states at each transition stage. **C.** Duration of Up states and MA versus their onset time. **D.** Mean (solid line) and SD (shadow) of the Up state duration distribution averaged across experiments in each stage of the transition towards wakefulness. Boxplots as in Fig. 1F,G.

Figure 4. MA is not merely a longer Up state. A. Asymptotic FR of Up and MA states relative to the mean FR of the Down states computed in 1-min time windows. **B.** Population average of the asymptotic FR during Up and MA states at each transition stage. **C.** Population average of the mean asymptotic FR of Up states and MA during the part of the experiment in which SO and MA coexist (time from L1 to L2). For each subject, FR values were normalized by the value of asymptotic FR during Up states. Boxplots as in Fig. 1F,G.

Figure 5. Modeling awakening from deep anesthesia in a neuronal assembly. A. Top: sketch of the mean-field rate model of a cortical assembly reproducing *in vivo* recordings at varying levels of anesthesia. The model state variables are the FR $\nu(t)$ and its adaptation level $a(t)$ determining an activity-dependent inhibition current proportional to g_a. The excitability of the system is modulated by a linear combination of an oscillatory ($I_{\sin}$) and a constant (I_{ext}) external input current. Bottom: Bifurcation diagram (I_{ext}, g_a) with all the dynamical regimes the model is capable of expressing: a stationary attractor state at low (high) FR values in the LAS (HAS) region and an oscillatory state (stable limit cycle) in the SO region. In the bottom-left corner both high and low firing states coexist (bistable regime). Dashed line: parameter trajectory modeling the anesthesia changes from D1 to L2. Sinusoidal arrows: trajectory section where $I_{\sin}$ is added. **B**. Subcritical Hopf bifurcation close to the L2 level probed by changing I_{ext}, and associated by a (gray) interval where SO and HAS states coexist. Solid lines: maximum and minimum FR having a gap $\Delta\nu > 0$ under SO. Dotted lines: extensions of the unstable limit cycle separating SO and HAS manifolds. **C**. Phase portraits $(-g_a\, a, \nu)$ mirroring the planes (a, ν) of the modeled network representing different anesthesia levels: D1, D2 and L2 from top to bottom, respectively. Black and gray solid lines, nullclines $d\nu/dt = 0$ and $da/dt = 0$, respectively. Their intersections are stable (diamonds) or unstable (circles) fixed-points of the network dynamics. Example trajectories from the periods of time highlighted in (D) with same color code. The two example trajectories for L2 depicting the transition from SO to MA (MA) and vice versa (left and right, respectively). Dashed and solid $d\nu/dt = 0$ nullclines correspond to the maximum and minimum values of $I_{\sin}$, respectively. **D**. Representative network activity $\nu(t)$ simulated under the three dynamical regimes in (C). Bottom: time course of the oscillatory input $I_{\sin}$ incorporated to model L2. **E**. Spectrogram of the FR $\nu(t)$ as the network parameters are varied following the trajectory shown in (A) at constant speed. **F**. State duration (top) and average FR (bottom) of detected Up, Down and MA states in the same simulation shown in (E).

Figure 6. Similar fingerprints of attractor dynamics in model and experiments. A. Mean FR (ν in model, top and log(MUA) in experiments, bottom) of Down-to-Up and Down-to-MA transitions during light anesthesia level (L1-like in model, and from L1 to L2 in experiments) normalized to the maximum FR during MA. Shadings: SD. **B**. Mean FR as in (A), but for Down-to-MA transitions divided in two groups with low and high FR at the end of the preceding Down state. Gray boxes: consecutive 100 ms intervals following the MA onset used in C-D. **C**. Correlation between mean and SD of FR computed at the activity peak of each MA group in (B). Squares and dots represent average and single values, respectively. Dashed line: linear regression of all data points. ρ: Pearson correlation. **D**. Correlation between mean and SD of FR as in (C) but computed during each time interval highlighted by the shaded boxes in (B). Error bars: SD. Data from 5 simulations (model) and 4 rats (experiments).

Figure 7. Modeling the autonomous emergence of SO-MA state alternation. A. Infra-slow oscillation between SO and MA states can result from the interplay between cortical assemblies and subcortical regions (red and black circles, respectively) through mutual inhibition (dashed gray arrows). **B**. Autonomous dynamics of a population rate model of a cortical L5 assembly (red), receiving an additional inhibitory input $I_{\mathrm{BS}}(t)$ proportional to the activity $\nu_{\mathrm{BS}}(t)$ of subcortical regions (black). The strength $g_a(t)$ of adaptation currents in L5 assemblies is also affected by $\nu_{\mathrm{BS}}(t)$ to model the subcortical neuromodulation. This bidirectional coupling gives rise to a quasi-periodic crossing of the boundary between SO and HAS phase displayed in Fig. 5B (as a subcritical Hopf bifurcation) providing a parsimonious alternative to $I_{\sin}$. SO-MA state alternation in the $(I_{\mathrm{BS}}, g_a, \nu)$ subspace appears as two nested oscillations (left). **C**. Same as panel B, but with a smaller I_{ext}. While in panel B a larger I_{ext} leads to longer MA states like in level L2, a smaller I_{ext} produces longer periods of SO (gray shaded intervals), thus modeling the level L1 of anethesia.

STAR Methods

RESOURCE AVAILABILITY

Lead Contact

Further information and requests for resources should be directed to and will be fulfilled by the corresponding author, Núria Tort-Colet (nuria.tort-colet@cnrs.fr).

Materials Availability

This study did not generate new unique reagents.

Data and Code Availability

Source data for the figures in the paper is available at doi:10.17632/wh7vfyyyp2.1.

EXPERIMENTAL MODEL AND SUBJECT DETAILS

In vivo experiments were conducted on $n = 5$ adult male Wistar rats weighting an average of 271 ± 31 g. Animals were housed in polysulfone cages (48.2 cm x 26.7 cm x 21 cm with a floor area of 940 cm^2), preferentially in pairs from the same breed, with access to food and water ad libitum, and kept under 12 h light/dark cycle. All experiments were supervised and approved by the University of Barcelona Ethics Committee and complied with the Spanish regulatory laws (BOE 34/11370-421, 2013) and the European Union directive 2010/63/EU.

METHOD DETAILS

In vivo *LFP recordings and data analysis*

Subjects were anesthetized via an intraperitoneal injection of ketamine (60 mg/kg) and medetomidine (0.5 mg/kg) following the same anesthesia protocol as in Bettinardi et al. (2015) (different dataset). After the induction of anesthesia the rat underwent surgery to introduce a 16-channel silicon probe (1 shank with 16 linearly spaced sites at 100 μm increments with impedances of $0.6 - 1$ $M\Omega$ at 1 kHz from NeuroNexus Technologies) perpendicular to the surface of the right primary visual cortex (V1, -7.3 mm antero-posterior and 3.5 mm medio-lateral relative to bregma (Paxinos and Watson, 2004)) until the most superficial recording site was aligned with the cortex surface as in Amigó et al. (2015) and Mattia et al. (2021). The local field potential (LFP) at different depths (layers) of V1 was continuously recorded until waking signs appeared (withdrawal reflex, elevated heart rate, fast breathing or whisking) and a reinduction dose was administered to return to the initial deep level of anesthesia (data not shown).

To account for the inter-subject variability in the duration of the anesthesia protocol, we selected four intervals of 10 min at different levels of decreasing anesthesia in each experiment (see Fig. 1A). We took Deep1 (D1) as the first 10 min of recording, starting 44 ± 2 min after induction on average. The appearance of the first micro-arousal occurred, on average, 185 ± 35 min after induction. Deep2 (D2) was identified as the last 10 min of pure slow oscillations (SO) before that first micro-arousal, and the following 10 min corresponded to the Light1 (L1) interval. Finally, the last 10 min of recording before the reinduction were identified as the Light2 (L2) interval.

Atropine (0.05 mg/kg) was injected subcutaneously to prevent secretions. All pressure points and tissues to be incised were infiltrated with lidocaine before surgery. Body temperature was maintained at 37°C using a water-circulating heating pump. Electroencephalogram and electrocardiogram were monitored during the experiment. Heart rate values remained stable between 290 and 300 bpm.

LFPs (by LFP here we refer to the unfiltered signal, in mV) from different layers of V1 were simultaneously acquired at a sampling frequency of 9921 Hz during the fading of anesthesia and saved in consecutive 900-s-long recordings. Signals were amplified with a multichannel system (Multi Channel Systems) and digitized with a CED acquisition board and Spike2 software (Cambridge Electronic Design).

For each channel, multi-unit activity (MUA) was estimated as the power of the Fourier components at high frequencies ($200 - 1500$ Hz) of the extracellular recordings (LFP) in windows of 50 ms (Reig et al., 2010; Sanchez-Vives et al., 2010; Mattia et al., 2010; Ruiz-Mejias et al., 2011) (Fig. S1). MUAs were logarithmically scaled and their values were shifted to center the first peak of the bimodal distribution of log(MUA) values – which corresponds to the Down state MUA values– at $\log(MUA) = 0$. As shown in Mattia et al. (2010), this time series provides an accurate estimate of the population FR because normalized Fourier components at high frequencies have densities proportional to the spiking activity of the involved neurons.

Periods with high and low FR were singled out by setting a threshold in the $\log(MUA)$ time series at one-third of the interval between the peaks of the bimodal distribution of $\log(MUA)$ values and a minimum state duration of 80 ms. Low FR periods were classified as Down states, while the remaining high FR periods were further classified as Up states or micro-arousal states if they took place during a sufficiently high or low value of the LFP moving variance, respectively. We computed the moving variance of the LFP in windows of 1 s with 0.1-s steps. For each experiment, a threshold to distinguish between Up state or micro-arousal was set at 15% of the distribution of the moving variance of LFP values of those recordings with pure slow oscillatory activity (recordings before L1 onset).

In this study we selected, in each experiment, the channel with maximum FR (asymptotic FR, see below) during the Up state since in V1 of mice (Senzai et al., 2019) and rats (Mattia et al., 2021) the maximum LFP power at high frequencies is consistently found in L5.

Population rate model

We considered the mean field dynamics of a population of $N = 1000$ excitatory, recurrently connected (probability of connection: $C = 0.3$, synaptic weights: $J = 0.1$ mV) leaky integrate-and-fire (LIF) neurons affected by activity-dependent self-inhibition (adaptation) $a(t)$, whose strength

is defined by the coupling variable g_a, and an external input current, I_{ext}, modeling the average excitatory synaptic input provided by presynaptic neurons external to the modeled network.

The external input is received by a number $C_{ext} = 500$ of external Poisson neurons with an average FR ν_{ext} that is varied to explore the different values of I_{ext} and connected through a synaptic weight $J_{ext} = 1.6$ mV:

$$I_{ext} = \nu_{ext} C_{ext} J_{ext} \,. \tag{1}$$

We also considered an additional oscillating input current, I_{sin}, that under suitable dynamical conditions can be turned on to reproduce the alternation between micro-arousals and SO observed under light anesthesia. This oscillatory external input is defined as:

$$I_{\sin}(t) = A \sin^2(\pi t/T) \tag{2}$$

where $A = 720$ mV/s and $T = 7$ s are the amplitude and the period of oscillation chosen to fit the experimental observations.

The dynamics of the population can be defined by the following first-order ordinary differential equations:

$$\begin{cases} \tau_\nu \dot{\nu}(t) = \Phi[\nu(t), a(t), g_a, I_{ext} + I_{\sin}] - \nu(t) + \varepsilon\xi(t) \\ \dot{a}(t) = -\frac{a(t)}{\tau_a} + \nu(t) \end{cases}, \tag{3}$$

where Φ is the input-output gain function for the LIF neuron (Johannesma, 1968; Ricciardi and Sacerdote, 1979), $a(t)$ is the adaptation variable, $\nu(t)$ is the FR, $\xi(t)$ is a Gaussian white noise modeling the activity fluctuations due to the finite number of neurons (finite-size) composing the network. These fluctuations are state dependent (Mattia and Del Giudice, 2002) and here are modeled as an activity-dependent SD $\varepsilon(t) = 0.225\nu(t) + 1.5$. As a result, $\nu(t)$ is a stochastic process. Decay times for ν and a are respectively $\tau_\nu = 20$ ms and $\tau_a = 500$ ms.

The input-output gain function can be explicitly expressed as in (Brunel, 2000; Ricciardi, 1977):

$$\Phi(\mu, \sigma^2) = \left[\tau_{arp} + \tau_\nu \sqrt{\pi} \int_{\frac{V_r - \mu\tau}{\sigma\sqrt{\tau}}}^{\frac{\theta - \mu\tau}{\sigma\sqrt{\tau}}} e^{u^2} (1 + \mathrm{erf}(u)) du \right]^{-1}, \tag{4}$$

where $\tau_{arp} = 5$ ms is the absolute refractory period, which defines the maximum FR ($\nu_{max} = \frac{1}{\tau_{arp}}$), τ is the decay constant of the LIF membrane potential, $V_r = 0$ is the reset potential, $\theta = 1$ is the spiking threshold, $\mathrm{erf}(u)$ is the error function, and the infinitesimal mean and variance of the input current (μ and σ^2) are defined as:

$$\begin{cases} \mu = \nu NCJ + I_{\mathrm{ext}} + I_{\sin} - g_a\, a(t) \\ \sigma^2 = \nu NCJ^2 + \nu_{ext} C_{ext} J_{ext}^2 \end{cases}. \tag{5}$$

This dynamic mean-field approximation provides an effective description of the collective dynamics of networks composed of LIF neurons with spike-frequency adaptation even far from equilibrium (Gigante et al., 2007), as in the conditions explored here with limit cycles (SO) and crossings of critical points.

The network dynamics can be modulated by changing the values of the adaptation strength (g_a) and the external current (I_{ext}).

The nullclines of the adaptation ($da/dt = 0$) and the activity ($d\nu/dt = 0$) were evaluated and their intersections identified as fixed-points.

Stable fixed points correspond to regions in the (I_{ext}, g_a) parameter space (Fig. 5A) in which there is an attractor state at low (LAS) or high (HAS) activity level, while unstable fixed points corresponding to an oscillatory regime are represented in the SO region.

To simulate the decrease in the anesthesia level we progressively increased the external input (I_{ext}) and decreased the adaptation strength (g_a), yielding the grey, dashed trajectory of Fig. 5A. Parameter values are specified in table 1.

Parameter	D1	D2	L1	L2
$I_{ext}(mV/s)$	320	1480	1920	2170
$g_a(mV/s)$	200	137	114	100

Table 1. Parameter values at each simulated level of anesthesia.

By introducing the $I_{sin}(t)$ current it is possible to have the regular alternation between SO and HAS dynamics observed in the experiments during L1 and L2.

The transition between HAS and SO is *via* a Hopf bifurcation and can happen in two ways: *i*) the limit cycle is created with an infinitesimal amplitude while the fixed point becomes unstable, or *ii*) with a finite one while the fixed point is still stable. The two kinds of transitions are referred to as super-critical and sub-critical Hopf bifurcations respectively (Strogatz, 2014). In this paper we claim that the data are well reproduced by a sub-critical Hopf bifurcation, which constrained the trajectory we chose from D1 to L2.

To further investigate the nature of this bifurcation, we evaluated the activity level of the network at a constant adaptation strength $g_a = 100$ mV/s while slowly changing the external current I_{ext} from 2365 mV/s to 2450 mV/s (Fig. 5B), and evaluating the amplitude of the oscillations (maximum and minimum value of the dynamics). The same was done in the opposite direction, decreasing the external current I_{ext} from 2450 mV/s to 2365 mV/s.

The presence of an hysteresis proves the existence of an interval where SO and HAS states coexist (Fig. 5B gray region). This demonstrates that the nature of the Hopf transition is sub-critical.

Population rate model for autonomous SO-MA state alternation

To model the infra-slow oscillations between SO and micro-arousal states by an autonomous system we considered the input $I_{\sin}$ as due to the activity ν_{BS} of a subcortical structure

(e.g., a cholinergic nucleus in the brainstem such as the pedunculopontine tegmental nucleus), and the adaptation strength g_a was modeled to be time-dependent to incorporate the neuromodulatory effect of the same subcortical projections. To close the loop, $\nu_{BS}(t)$ integrated the cortical activity $\nu(t)$ as follows:

$$\begin{cases} \tau_\nu \, \dot{\nu}(t) = \Phi[\nu, a, g_a, \nu_{BS}] - \nu(t) + \varepsilon \, \xi(t) \\ \dot{a}(t) = -\dfrac{a(t)}{\tau_a} + \nu(t) \\ \tau_{BS} \, \dot{\nu}_{BS}(t) = -\nu_{BS}(t) + \nu(t) - \nu_0 \\ \dot{g}_a(t) = -\dfrac{g_a(t) - \bar{g}_a}{\tau_{BS}} + \nu_{BS}(t) \end{cases}, \quad (6)$$

where $\tau_\nu = 22.6$ ms, $\tau_a = 0.5$ s, $\tau_{BS} = 20$ s, $\nu_0 = 68.4$ Hz and $\bar{g}_a = 433$. As above, $\xi(t)$ is a Gaussian white noise with infinitesimal SD $\varepsilon = 0.14$.

As in Eq. (3), the input-output gain function Φ returns the stationary FR of neurons receiving the following mean input current

$$\mu(\nu, a, g_a, \nu_{BS}) = \nu NCJ + I_{ext} + I_{BS}(t) - g_a(t)\, a(t), \quad (7)$$

where N, C and J are the same as above, and the infinitesimal variance σ^2 is the same as in Eq. (5). The input current from the brainstem to the cortical population is $I_{BS}(t) = -g_{BS}\, \nu_{BS}(t)$ with $g_{BS} = 10$ mV.

The different levels of anesthesia (L1 and L2) are obtained by setting an increasing $I_{ext} = C_{ext}\, \nu_{ext}$ with $\nu_{ext} = 15.3$ Hz for the deeper (L1) and $\nu_{ext} = 16.5$ Hz for the lighter level (L2). In both cases $C_{ext} = 500$.

QUANTIFICATION AND STATISTICAL ANALYSIS

To evaluate the average FR during Up or micro-arousal states we computed the asymptotic FR discarding the initial and final 50 ms values of MUA to avoid averaging values during the transitions and conserving only those states in which the remaining time was at least 100 ms.

Power spectra were computed using the Welch method, and spectrograms were computed in non-overlapping windows of 1-min using the LFP signal high passed at 0.01 Hz.

The evolution of the duration or the FR of the different states (Up, Down, micro-arousal) across the decreasing levels of anesthesia was evaluated by averaging the values of state duration or FR in time windows of 1 minute across the time of each experiment. To compare between subjects, we used the average value of duration or FR of the states that fell into the time intervals selected as D1, D2, L1 or L2 in each experiment.

Statistical significance was set at $p < 0.05$. The statistical test applied is specified in each case either in the results section or in the figure legends. n corresponds to the number of subjects unless otherwise stated.

In order to understand the dynamical nature of micro-arousals, we evaluated the average profile of the $\log(MUA)$ around the Down-to-micro-arousal transition over all micro-arousals in each recording. In order to average over different recordings, we rescaled the $\log(MUA)$ to have its minimum as 0 and its maximum as 1:

$$\log(\mathrm{MUA})_{norm} = \frac{\log(\mathrm{MUA}) - \log \mathrm{MUA}_{min}}{\log \mathrm{MUA}_{max} - \log \mathrm{MUA}_{min}}, \quad (8)$$

where $\log \mathrm{MUA}_{max}$ and $\log \mathrm{MUA}_{min}$ are respectively the maximum and the minimum of the profile averaged over all micro-arousal states in a single experiment. Once normalized, $\log(MUA)_{norm}$ was averaged over all recordings. In each experiment, micro-arousals were sorted by level of activity in the Down state before the micro-arousal onset and grouped into three clusters of the same size. In each cluster the average profile of the normalized $\log(MUA)$ was computed with Eq. (8) and using the same $\log \mathrm{MUA}_{max}$ and $\log \mathrm{MUA}_{min}$ as estimated above. Finally, the average profile around the Down-to-Up transition from the L1 to L2 periods was estimated and normalized.

As an indicator of the attractor state stability we resorted to the inter-state variability of the normalized $\log(\mathrm{MUA})$ as follows:

$$\mathrm{MUA}\, SD_{norm} = \frac{\mathrm{MUA}\, SD}{\log \mathrm{MUA}_{max} - \log \mathrm{MUA}_{min}}. \quad (9)$$

In this analysis, one out of five experiments was rejected as the MUA signal was extremely noisy, probably due to the electrode placement. This led to profiles of single micro-arousals that were not good enough for a dynamical fine structure analysis.

All analyses were performed using MATLAB (The MathWorks).

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