Convergent effects of different anesthetics are due to changes in phase alignment of cortical oscillations

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Abstract

Many different anesthetics cause loss of responsiveness despite having diverse underlying molecular and circuit actions. To explore the convergent effects of these drugs, we examined how ketamine, an N-methyl-D-aspartate (NMDA) receptor antagonist, and dexmedetomidine, an α2 adrenergic receptor agonist, affected neural oscillations in the prefrontal cortex of nonhuman primates. Previous work has shown that anesthesia increases phase locking of low-frequency local field potential activity across cortex. We observed similar increases with anesthetic doses of ketamine and dexmedetomidine in the ventrolateral and dorsolateral prefrontal cortex, within and across hemispheres. However, the nature of the phase locking varied between regions. We found that oscillatory activity in different prefrontal subregions within each hemisphere became more anti-phase with both drugs. Local analyses within a region suggested that this finding could be explained by broad cortical distance-based effects, such as a large traveling wave. By contrast, homologous areas across hemispheres increased their phase alignment. Our results suggest that the drugs induce strong patterns of cortical phase alignment that are markedly different from those in the awake state, and that these patterns may be a common feature driving loss of responsiveness from different anesthetic drugs.

Introduction

Many different anesthetics exist and are widely used in medicine for similar purposes, despite having distinct mechanisms of action. The common elements by which these drugs induce similar outcomes, namely loss of responsiveness, is an open question[1,2]. Their convergence is likely at a higher level, in the network dynamics driven by each drug's unique molecular effects. Here, we explored the idea that different anesthetics may cause loss of responsiveness via similar effects on cortical synchrony.

To address the question of functional convergence we examined ketamine and dexmedetomidine, two anesthetics with distinct molecular actions on different pathways. Ketamine strongly affects cortex by antagonizing N-methyl-D-aspartate (NMDA) receptors. By contrast, dexmedetomidine agonizes α2 adrenergic receptors, mainly in the locus coeruleus. At anesthetic doses, they both produce the same behavioral outcome: loss of responsiveness.

We examined bilateral recordings from prefrontal cortex (PFC) of macaques during administration of ketamine and dexmedetomidine. We quantified cortical synchrony, which is thought to play a role in consciousness[3–7]. We explored not only phase locking, a common measure of the consistency of local field potential (LFP) signals between different areas, but also the phase offsets at which these LFPs were locked.

We found evidence that ketamine and dexmedetomidine had similar effects in how they changed phase relationships between low-frequency LFPs. The drugs increased phase locking across all recorded regions of prefrontal cortex, but the nature of this phase locking was not homogeneous. Between different regions within a hemisphere, the drugs both induced consistently misaligned LFP activity, while between homologous regions across hemispheres, they caused activity to become more aligned. These shifts suggest that anesthetics act through complex changes in phase alignment of oscillatory dynamics that are common across drugs despite their different molecular actions.

Results

We examined activity simultaneously recorded from electrode arrays in the right dorsolateral and ventrolateral PFCs (R-Dor and R-Ven, respectively) and left dorsolateral and ventrolateral PFCs (L-Dor and L-Ven, respectively). A lever-pressing task, which involved pressing a lever for a reward whenever a tone was played, was used to assess loss of responsiveness. The task was run before anesthetic drug administration, around the time of administration, and during the period of unresponsiveness induced by the anesthetics. The lever pressing task occurred during periods with a white background in Figure 1A. Anesthetic doses of ketamine (10 mg/kg) and dexmedetomidine (20 mg/kg) caused monkeys to stop responding (black dots indicate responses, Fig. 1A) shortly after their administration (vertical black line at time zero, Fig. 1A), indicating the onset of anesthetic effects. For all the following analyses, neural data was taken from periods during which the lever-pressing task was not happening (gray boxes, Fig. 1A), to minimize differences between before- and during-anesthetic periods due to movement and reward. Animals remained unresponsive even after the lever task was reinstated at 25 min post drug.

Anesthetics increased low-frequency power

Ketamine and dexmedetomidine at anesthetic doses increased low-frequency LFP power. Figure 1B shows the spectrogram of LFP power from one channel of one array around the administration of anesthetics for a representative session from each drug type. Across all sessions, both drugs caused an increase in power below 16 Hz that was especially prominent in the delta (1-4 Hz) and theta (4-8 Hz) bands (Fig. 1C). Ketamine also caused an increase in gamma band power (30-100 Hz), while dexmedetomidine caused a slight decrease (Fig. 1C).

Fig. 1

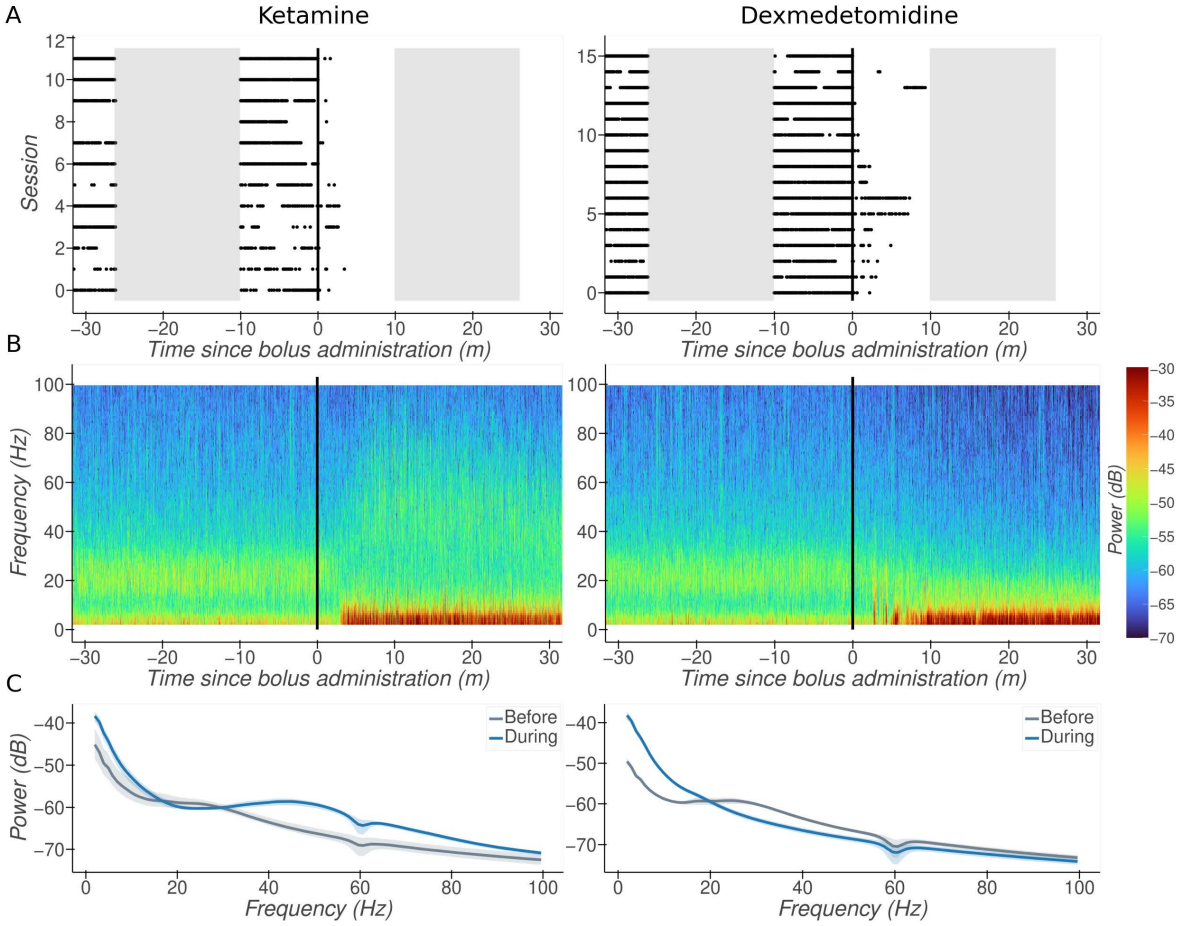

Figure 1: Both anesthetics induced loss of responsiveness, increased low-frequency power. (A) Behavioral response to the lever-pressing task. Black dots indicate lever presses; black line at time 0 indicates drug administration. Gray areas indicate time periods without the lever task (further analysis focuses on data from this period). (B) LFP power as a function of frequency and time for two representative sessions (single channel), one with ketamine (left) and one with dexmedetomidine (right). Black line at time 0 indicates drug administration. (C) Average LFP power across all sessions before (gray) and during (blue) anesthetics. Significant differences between conditions correspond to frequencies where confidence intervals do not overlap ($p < 0.01$). The notch effect at 60 Hz is due to filtering of line noise in sessions for one animal (not the animal shown in part B).

Anesthetics increased LFP phase locking

Both drugs caused an increase in phase locking at low frequencies. Figure 2A shows phase locking, as measured by the phase-locking value (PLV), before drug delivery. It shows average phase locking between LFPs from all possible pairs of electrodes in the four arrays implanted in

the left and right dorsolateral and ventrolateral PFC. Here and elsewhere, comparisons within hemispheres are colored green and those across hemispheres are colored purple (Fig. 2).

After drug delivery, there was a significant increase in average phase locking at low frequencies (1-8 Hz) between the dorsolateral and ventrolateral PFC within each hemisphere, as well as across the two hemispheres (Fig. 2B). Figure 2C shows the change in phase locking caused by the drugs. The increase indicated that the relative phase between pairs of LFPs was becoming more consistent. Note that this increase in phase locking did not necessarily mean the phases were aligned, a point we will take up below. There was a slight dip in phase locking within a hemisphere for both drugs in the 20-40 Hz range, and a slight increase for ketamine in the 40-60 Hz range, but these effects were much smaller than those seen at the low frequencies.

We confirmed this effect using another measure of phase locking, coherence. PLV measures phase locking independent of changes in power[8–10]. Coherence takes into account both phase and power to measure how linearly predictable one signal is from another. This analysis yielded similar results: an increase in signal consistency at low frequencies (Fig. S1A). The effects were similar for all combinations of the arrays, both within hemispheres (R-Dor vs. R-Ven, L-Dor vs. L-Ven) and across hemispheres (R-Dor vs. L-Dor and R-Ven vs. L-Ven) (Fig. S1A). They were also similar for the "diagonal" comparisons across both subregions *and* hemispheres (R-Dor vs. L-Ven and L-Dor vs. R-Ven) (Fig. S1B-C). These effects were largely consistent across different sessions and across the two monkeys (Fig. S2A-B).

Fig. 2

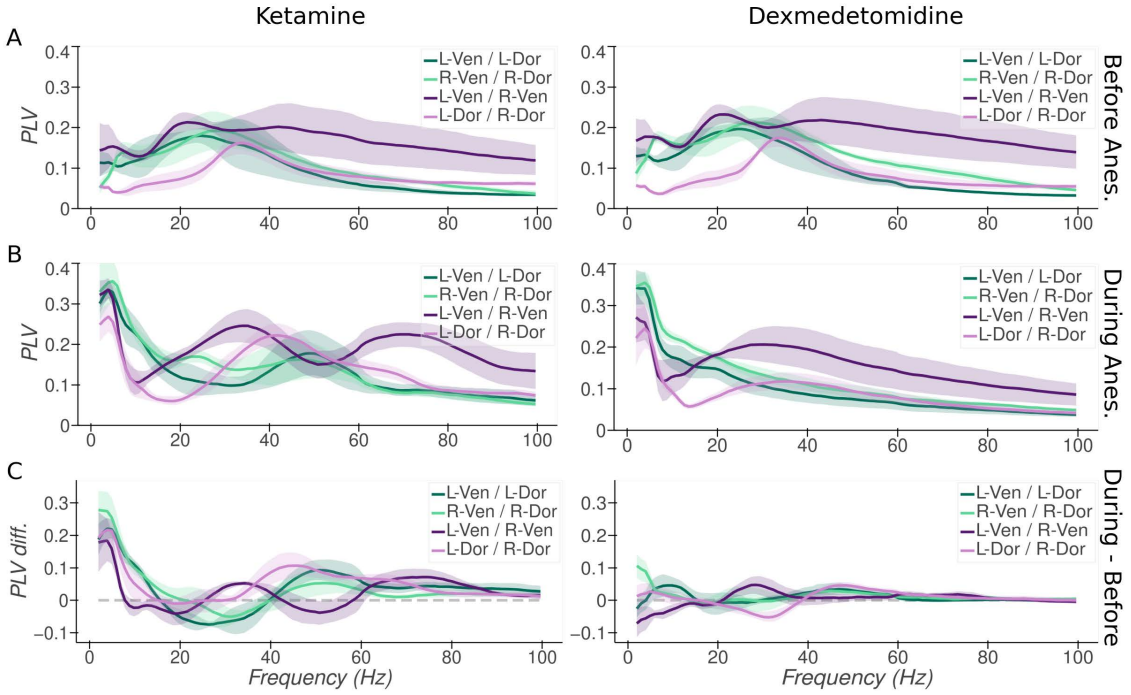

Figure 2: Anesthetics increased LFP phase locking. Phase-locking value (PLV) between channels in pairs of arrays (shading shows 99% confidence intervals across sessions). (A) Before anesthetics, (B) during anesthetics, (C) their difference (during – before).

Anesthetics misaligned activity within hemispheres but aligned it across hemispheres

The increase in low-frequency phase locking caused by ketamine and dexmedetomidine at anesthetic doses did not necessarily mean that the phases became more aligned. We found that the phase offsets became more anti-phase within hemispheres and more in-phase across hemispheres.

Figure 3A and B show the distribution of phase offsets in the 1-4 Hz range. The gray bars show the phase offsets before drug delivery. They varied across comparisons between areas and hemispheres, ranging from nearly uniform to biased toward in-phase (0° offset) or anti-phase (180° offset). The left and right ventrolateral PFC in particular had a bias towards anti-phase offsets during wakefulness for both drugs (Fig. 3A-B), across all frequencies (Fig. S3A). The colored bars show phase offsets after anesthetic administration. They indicate an increase in anti-phase offsets between ventrolateral and dorsolateral arrays (L-Ven vs. L-Dor, R-Ven vs. R-Dor; Fig. 3A-B, green). By contrast, there was increased phase alignment across hemispheres (L-Ven vs. R-Ven, L-Dor vs. R-Dor; Fig. 3A-B, purple).

The changes in phase offsets were mainly in the lower frequencies. To quantify this effect, we calculated a phase alignment index, measuring the average cosine of the phase offsets. Figure 3C shows the change in the phase alignment index with anesthetics (non-subtracted values before and during anesthetics shown in Fig. S3). Anesthetic doses of both ketamine and dexmedetomidine caused a significant decrease in phase alignment within hemispheres (negative alignment index, more towards 180°) at frequencies below 12 Hz (Fig. 3C, green lines). Across hemispheres, there was a significant increase in phase alignment (positive alignment index, more towards 0°) for the same frequency range (Fig. 3C, purple lines). The effects were consistent across animals, sessions, and drugs (Fig. S4). Along the diagonal comparisons (L-Ven vs. R-Dor, R-Ven vs. L-Dor) we also found a slight increase in anti-phase signals (Fig. S5).

Fig. 3

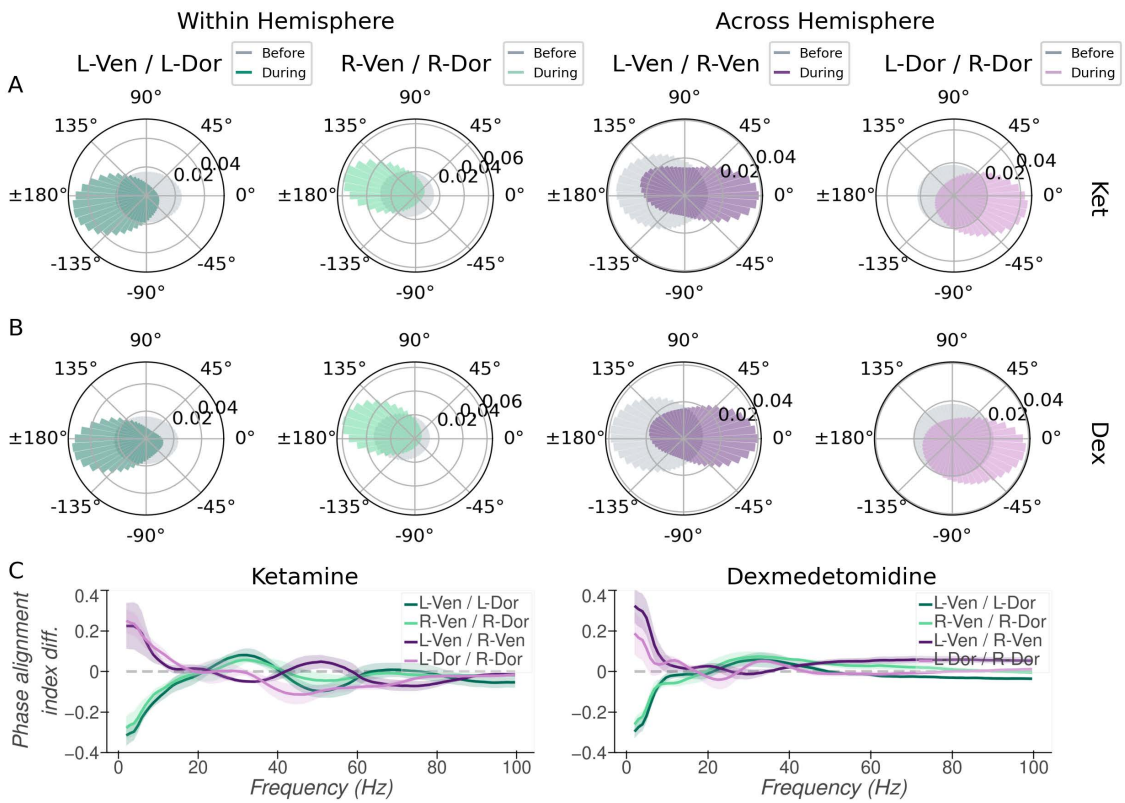

Figure 3: Anesthetics increased phase offsets within hemispheres, decreased across hemispheres. (A-B) Histogram of phase offsets between all channel pairs in indicated regions before (gray) and during (colored) anesthetics for (A) ketamine and (B) dexmedetomidine in the 1-4 Hz range. (C) Phase alignment index cos(Δϕ) (0° offset is +1, 180° offset is -1, uniform offset averages to zero) difference (during – before anesthetics) (shading shows 99% confidence intervals across sessions).

Increased phase offset with distance was amplified by anesthetics

To explore whether the observed cross-region phase offsets could be explained by distance effects, we quantified how the phase locking and phase offsets changed with distance within an array, where precise relative locations of recording sites were known. We found that in the awake PFC, phase locking decreased and phase offset increased with distance within each recording array. These effects were stronger with anesthetics. The phase locking and phase offsets were relatively linear as a function of distance (example of low-frequency PLV in Fig. 4A), so we also examined the slopes of these lines.

Before drug delivery, Figure 4A (gray lines) shows that phase locking decreased with electrode distance within each array in the low-frequency range (1-4 Hz). Figure 4B (gray lines) shows that this effect existed across a wide range of frequencies (decrease indicated by negative slopes). Phase offset with distance was almost flat before drug delivery for the low frequencies

(gray lines, Fig. 4C). By contrast, the mid-range frequencies (15-40 Hz) showed marked increase in phase offset with distance before drug delivery (Fig. 4D), likely due to the greater relative power of mid-range frequencies during the awake state.

Both ketamine and dexmedetomidine amplified these trends. At low frequencies, the drugs caused a sharper decline in phase locking and sharper increase in phase offset with distance (Fig. 4B, D). Note that there are fewer pairs in an array at farther distances, which could lead to greater variability at those higher distance measurements, in addition to the decreased phase locking at those distances. At higher frequencies, the results were mixed. The effect of ketamine on phase locking in the gamma band (40-100 Hz) was similar to low frequencies (Fig. 4B). Dexmedetomidine, by contrast, caused a flattening of the slope of PLV vs. distance between 30-70 Hz. Neither drug had large effects on the overall phase offsets at high frequencies.

A continuation of these distance trends amplified under drug influence could explain the phase offsets between arrays in ventrolateral and dorsolateral PFC. The cortical surface distance between these arrays was ~20 mm, so given the ~20°-30° phase offset between channels at either end of the array (~2.5 mm apart), extrapolating across distance could explain the observed ~180° phase offset across regions. The phase locking at the farthest distance within an array is still above values seen between arrays, but likely levels off at further distances.

Fig. 4

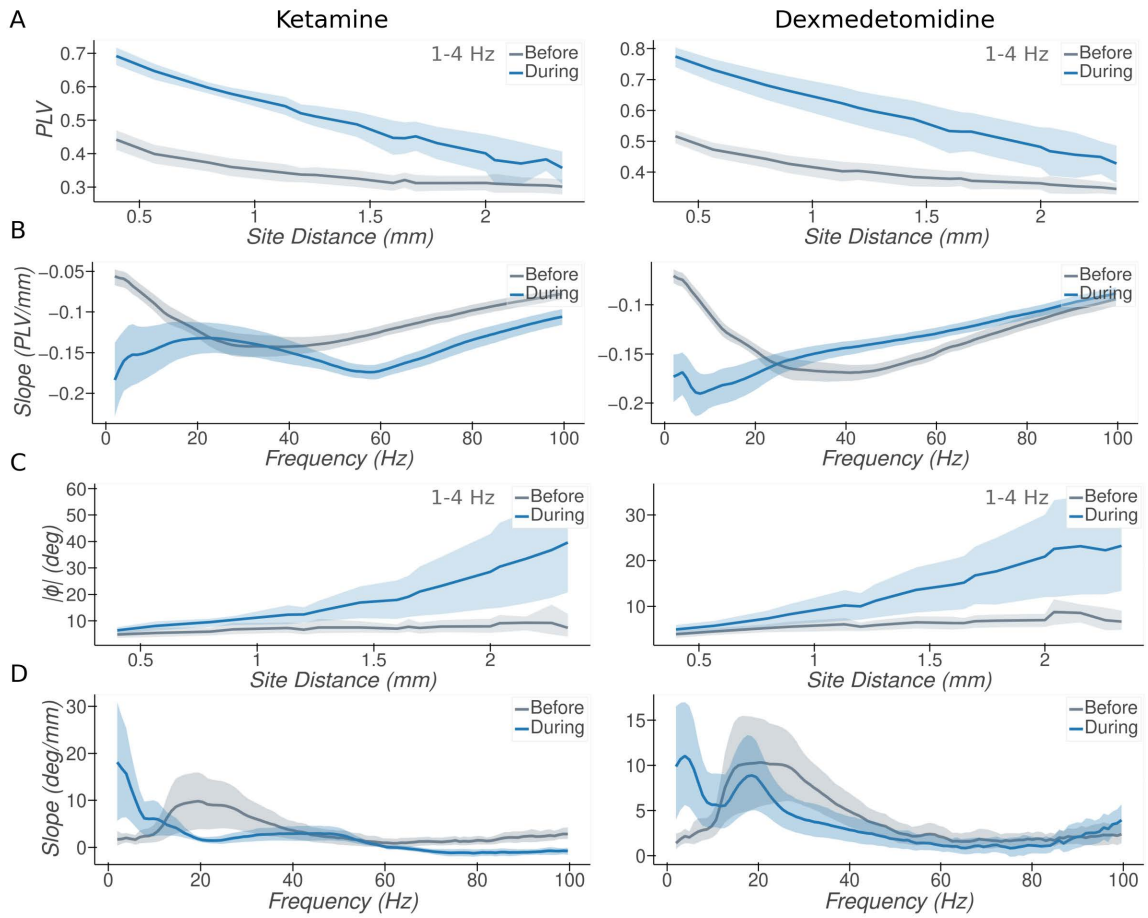

Figure 4: Phase locking weakened and LFPs became more anti-phase with distance. (A) PLV vs. distance within an array, before (gray) and during (blue) anesthetics, in the low-frequency range (1-4 Hz). (B) Slope of PLV vs. distance as a function of frequency. (C) Phase offset (absolute value) vs. distance (1-4 Hz). (D) Slope of phase offset (absolute value) vs. distance as a function of frequency (shading shows 99% confidence intervals across sessions).

Sub-anesthetic doses of ketamine and dexmedetomidine produced weaker effects

Sub-anesthetic doses of both drugs (1 mg/kg ketamine, 5 mg/kg dexmedetomidine) produced effects that were weak and more variable but trended towards those seen in anesthetic doses. For ketamine, there was no change in low-frequency power and a smaller increase in gamma power (Fig. 5A, left) than with the anesthetic dose. For dexmedetomidine, there was a smaller increase in low-frequency power than with the anesthetic dose (Fig 5A, right). Between arrays, there were smaller effects in phase locking with no consistent trends (Fig. 5B). Phase offsets were smaller with sub-anesthetic doses but trended in the same direction (Fig. 5C-D), and they reached significance for a smaller range of frequencies. Within the arrays, the local distance effects were reduced. Sub-anesthetic doses caused a smaller decrease in phase locking (Fig. 5E) and a smaller increase in phase offset (Fig. 5F) with distance than the anesthetic doses.

Fig. 5

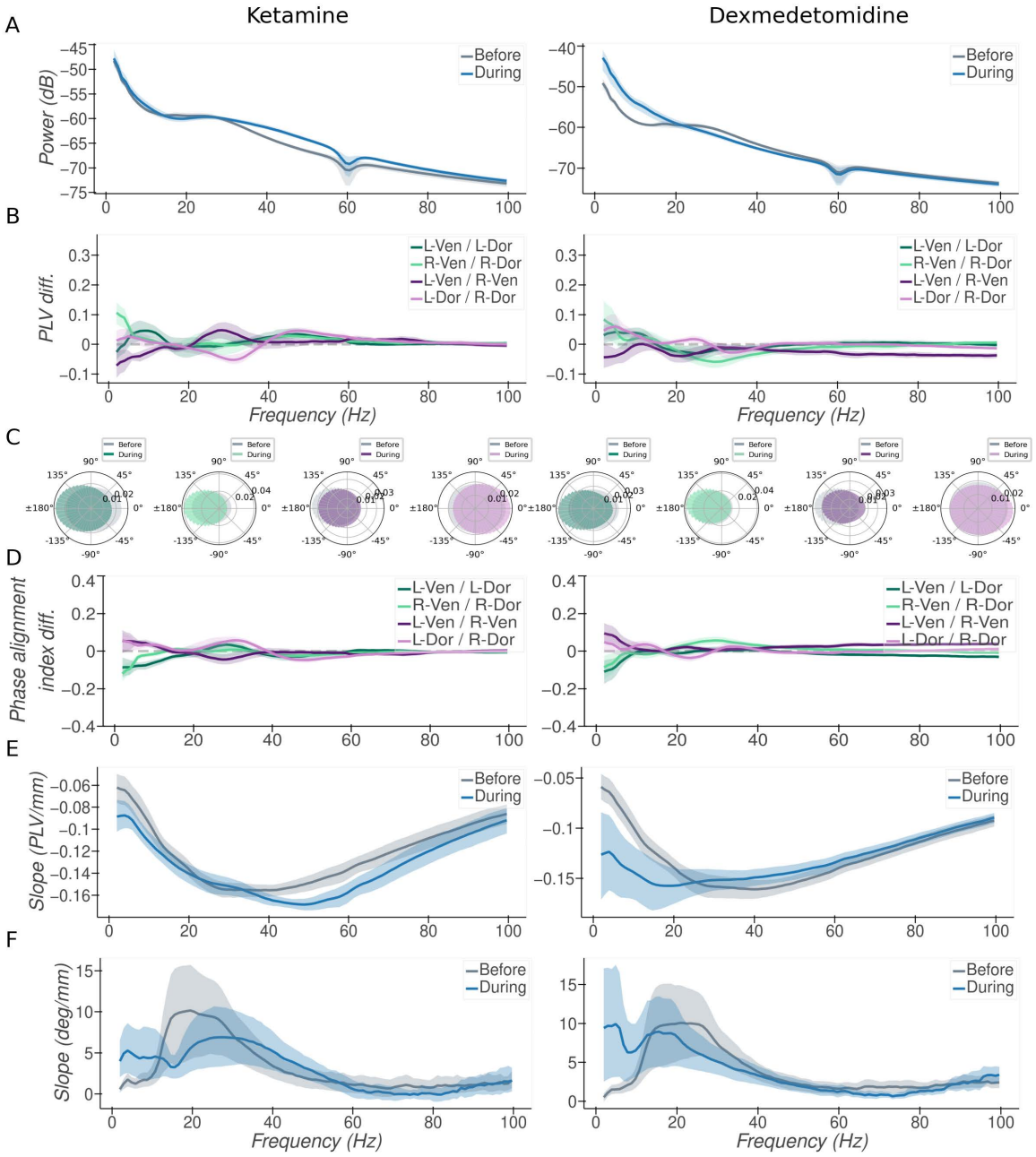

Figure 5: Sub-anesthetic doses of ketamine and dexmedetomidine have weaker, but qualitatively consistent, effects. (A) Average LFP power. (B) Change in PLV. (C) Histograms of phase offsets. (D) Change in phase alignment index. (E) Phase locking slope vs. frequency within array. (F) Phase offset (absolute value) slope vs. frequency within array (shading shows 99% confidence intervals across sessions).

Discussion

Ketamine and dexmedetomidine, while acting on different molecular and circuit pathways, induce similar changes in low-frequency oscillatory dynamics. These dynamics may be a marker of loss of responsiveness and suggest a fundamental role for broad, low-frequency activity in driving and disrupting consciousness.

We found that anesthetics heightened low-frequency cortical activity, misaligning this activity in different regions of PFC, while aligning it in homologous regions across hemispheres (Fig. 6). The drugs had different effects across different frequencies up to and including gamma, but the low frequency effects were the common feature between them. Increases in low-frequency power have been observed in cortical LFPs in animals and in electroencephalogram signals in humans for these drugs[11–16] as well as propofol, another anesthetic drug that is widely studied[17–22]. We also noted increased phase locking of LFPs both within and across hemispheres, an effect that has similarly been observed with propofol[21,22].

Fig. 6

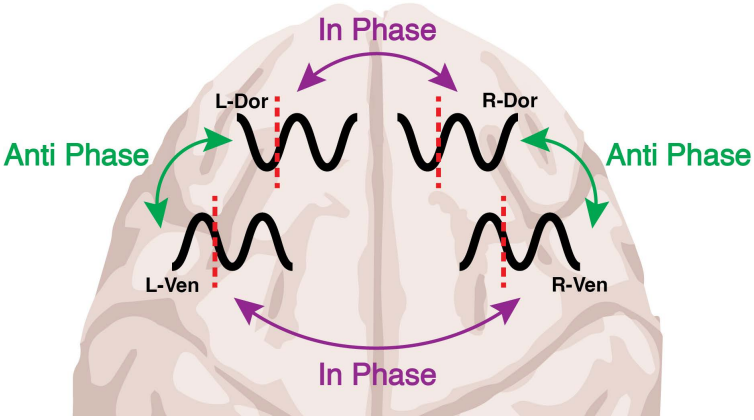

Figure 6: Anesthetics fragment cortical activity within a hemisphere but synchronize it across hemispheres. Ketamine and dexmedetomidine both cause phases of low-frequency oscillatory activity to become misaligned between different regions of PFC, and more aligned between homologous regions across hemispheres.

However, an increase in phase locking does not necessarily mean the signals are more aligned. Within a hemisphere, the ventrolateral and dorsolateral PFC became more anti-phase at low frequencies, with their phase offsets trending toward 180°. The low-frequency offsets that we observed were consistent across entire arrays, suggesting the observed effects come from spatially broad oscillations across cortex. Additionally, we found that extrapolating local phase-offset effects within a region across longer distances could explain the anesthetic-induced 180° phase offset between the ventrolateral and dorsolateral PFC. These effects could be due to a large traveling wave that moves between the areas.

Large-scale cortical traveling waves are known to occur spontaneously during anesthesia[23–25]. These waves may play an essential role in shaping neural activity when awake[26–29], and severely limiting it during anesthesia[25,30] by fragmenting within-hemisphere communication as periods of excitability become misaligned[3–7]. In fact, propofol has been shown to fragment activity and decrease information transfer across long distances (>2 cm) in human cortex[31–33], and to prevent sensory signals from reaching macaque frontal cortex[34]. We note that there was not a complete misalignment of phases at all times, but rather a tendency for LFPs to be out of phase more often. Such “relative coordination” can still strongly influence network activity[35].

In contrast to the observed fragmentation of activity within a hemisphere, we found that homologous regions across hemispheres became more aligned. The increase in interhemispheric alignment of activity by anesthetics seems to reverse the functional distinctions previously observed in the awake, cognitively-engaged brain. In that case, the two hemispheres are often able to function semi-independently, at least for visual cognition[36]. During quiet awake states and anesthesia, however, cross-hemispheric synchrony increases in mice[37], in line with our observations. This synchrony was found to be dependent upon the presence of the intact corpus callosum[37], which is known to preferentially connect homologous regions[38]. Such synchrony could also be mediated by subcortical inputs, such as those from the thalamus, a known hub of interhemispheric communication[39,40].

It is possible that our observations of low-frequency changes in LFP signals can be explained by the activity of cortical layer 5 pyramidal neurons, which anesthetics are known to influence[41–45]. These neurons make large contributions to the LFP and have low pass filtering properties at their somas[46–48]. Thus, they may play a significant role in the increases in power and phase locking of cortical slow-wave dynamics.

These neurons are also known to be a prominent component of thalamocortical loops[49]. The molecular effects of these drugs may cause loss of responsiveness via common disruptions to thalamocortical interactions[50,51], via both cortical and subcortical action. Thalamocortical connectivity is hypothesized to play a major role in consciousness[7,43,52–56] and in anesthetic-induced dissociation[57] or unconsciousness[21,22,58–64]. Experimental and modeling work show that low-frequency oscillations and thalamocortical connections may be involved in the transfer of information between cortical regions[65,66], and that such transfer may be disrupted during anesthesia, thus leading to unconsciousness[34,63,64]. Simultaneous recordings from and stimulation of cortex and thalamus during anesthesia will help to illuminate the role that these interactions play in driving the broad phase-offset activity that we found here.

Our results indicate that the loss of responsiveness caused by anesthetic doses of ketamine and dexmedetomidine results from changes not only in oscillatory power, but also in the alignment of low-frequency signals within and between cerebral hemispheres. These effects were severely weakened by sub-anesthetic doses of the drugs that were not sufficient to cause loss of responsiveness. Despite their different mechanisms of action at the molecular level, we found similar network-level effects between the two drugs. Thus, cortical network-level activity may be the optimal lens through which we can understand the convergent mechanisms of different anesthetics, and even make use of this understanding to inform anesthetic administration[67].

Methods

Experimental design

Ketamine and dexmedetomidine were administered as an intramuscular bolus to two monkeys (Monkey S and Monkey P) at sub-anesthetic (1 mg/kg ketamine - 13 sessions, 5 mg/kg dexmedetomidine - 16 sessions) and anesthetic (10 mg/kg ketamine - 12 sessions, 20 mg/kg dexmedetomidine - 16 sessions) doses. Induction of anesthetic effects was measured by loss of responsiveness in a lever-pressing task. In this task monkeys were trained to press a lever in response to a tone and received a juice reward for a correct response. All monkeys responded regularly before anesthetic injection, then stopped responding to the lever-pressing task before the period from which the “during anesthetic” data was taken for analysis. Changes in spectral LFP power consistent with known effects of ketamine and dexmedetomidine began around 3-4 minutes after anesthetics were injected (Fig. 1B) and could be seen throughout the period analyzed during anesthetics (Fig. 1C), which began 10 minutes after drug administration.

To study the effects of anesthetics on neural synchrony in PFC, neural activity was recorded continuously throughout the experiment (before, during, and after anesthetic injection) with chronically implanted Utah arrays placed in the left and right ventrolateral PFC and dorsolateral PFC (referred to as L-Ven, R-Ven, L-Dor, and R-Dor). Arrays were placed on either side of the principal sulcus but varied slightly in exact location and orientation. Each array had a regularly spaced grid of 6x6 electrodes, 400 micrometers apart (minus the four corner locations, for a total of 32 channels per array). In periods before and during anesthetics, the monkeys were presented with a separate passive auditory task, in which varying tones were played but monkeys were not required to respond. All analysis was performed on time periods during which the auditory task was happening. Results were indistinguishable during and between blocks of sounds within the auditory task period, so we pooled data across the entire period for analysis.

LFP processing

LFPs were recorded at 1kHz. For sessions with Monkey P, noise was removed at 60, 120, and 180 Hz with online notch filtering, resulting in a dip in power around 60 Hz (higher frequencies were not analyzed here). For Monkey S, filtering was performed offline, after data collection. LFPs were mean-subtracted (one global mean across all channels/arrays) at each timepoint to remove brain-wide noise, while preserving LFP relationships between arrays. Though many methods exist for removing noise from LFPs and each have different benefits and drawbacks[68,69], overall mean subtraction was most appropriate for the level at which we performed our analyses (studying region-wide differences across the cortex). To identify outlier channels, we calculated the standard deviation of the LFP from each electrode in a session. We then found the interquartile range of standard deviations for all channels in a session, and we removed channels with a standard deviation more than 5 interquartile ranges outside of the overall range, with an average of 3.8 channels out of 128 removed per session.

Spectral analysis

We used multitaper spectral estimation on a series of overlapping time windows to analyze data in the frequency domain. LFPs were split into 1 s time windows, beginning every 0.1 s (so each

window had 0.9 s overlap with the next one). We calculated the multitaper spectrogram[70–72] for each window using 5 tapers and a frequency width of 6 Hz over a total frequency range of 1-100 Hz.

PLV, coherence, phase offset

PLV, coherence, and phase offset were calculated between pairs of channels on indicated arrays. For a comparison between two given arrays, we analyzed all possible pairs of channels between the two arrays. We calculated the cross spectrum C_{XY} by multiplying signal X by the complex conjugate $Y^*$of signal Y (in the frequency domain) at each time window/taper between each channel pair. We also calculated auto spectra C_{XX} and C_{YY} by multiplying a signal by its own complex conjugate at each time window/taper. We then averaged over the tapers.

To calculate the PLV, we took the absolute value of the average normalized cross spectrum. To calculate coherence, we divided the cross spectrum of two channels by the square root of the product of each channel's auto spectrum. To calculate the phase offset, we took the angle of the cross spectrum. For within-array analyses, we took all possible pairings of channels within an array (excluding self-pairs) and then sorted the pairings by distance between sites.

$C_{XY} = X(f) \cdot Y^*(f)$, $C_{XX} = X(f) \cdot X^*(f)$, $C_{YY} = Y(f) \cdot Y^*(f)$

$PLV_{XY} = |C_{XY}|$

$Coh_{XY} = |\frac{C_{XY}}{\sqrt{C_{XX} \cdot C_{YY}}}|$

$\Delta\phi_{XY} = arg\ (C_{XY})$

PLV and coherence are dimensionless measures ranging from 0 to 1. Phase offsets range from -180° to 180°. All line plots show mean values with 99% confidence intervals. We first averaged across all channels or channel pairings for the indicated regions within a session. We then computed averages and nonparametric bootstrap confidence intervals across sessions (100,000 bootstrap replicates).

Phase histograms

Phase offset histograms show the distribution of phase offsets between all channel pairs in indicated regions, accumulated across all time points within a given recording period (before or during anesthetics). Phase offsets were calculated as indicated above and normalized by the total count of phase values contained in each histogram. The histograms have 50 bins, so bin values of 0.02 correspond to a uniform distribution across all phase offsets. The histograms show phase offsets for the 1-4 Hz frequency range.

Phase alignment index (as in Fig. 3C-E) was calculated by taking the cosine of each phase offset and averaging over time and channel pairs within a session. We chose to take the cosine of the phase offset because the peaks of the phase histograms tended towards 0° and 180°. In this metric, a circular uniform distribution of phases has an average value of zero, while distributions with more weight towards 0° or 180° have positive or negative values, respectively. Phase alignment index is a dimensionless measure ranging from -1 to 1.

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Supplementary Information

Fig. S1

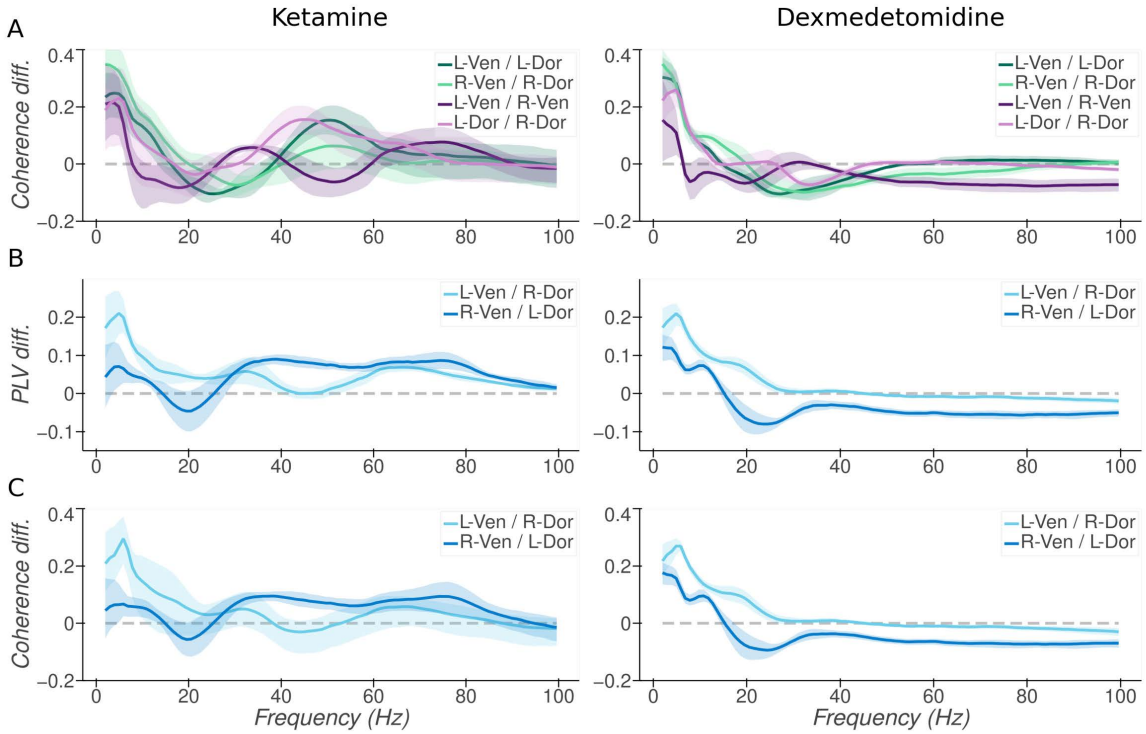

Figure S1: Results were consistent for coherence measure and for cross-area interhemispheric comparisons. (A) Coherence within and across hemispheres. (B) PLV for cross-hemisphere / cross-region pairs. (C) Coherence for cross-hemisphere / cross-region pairs. All plots show differences (during – before anesthetics) (shading shows 99% confidence intervals across sessions).

Fig. S2

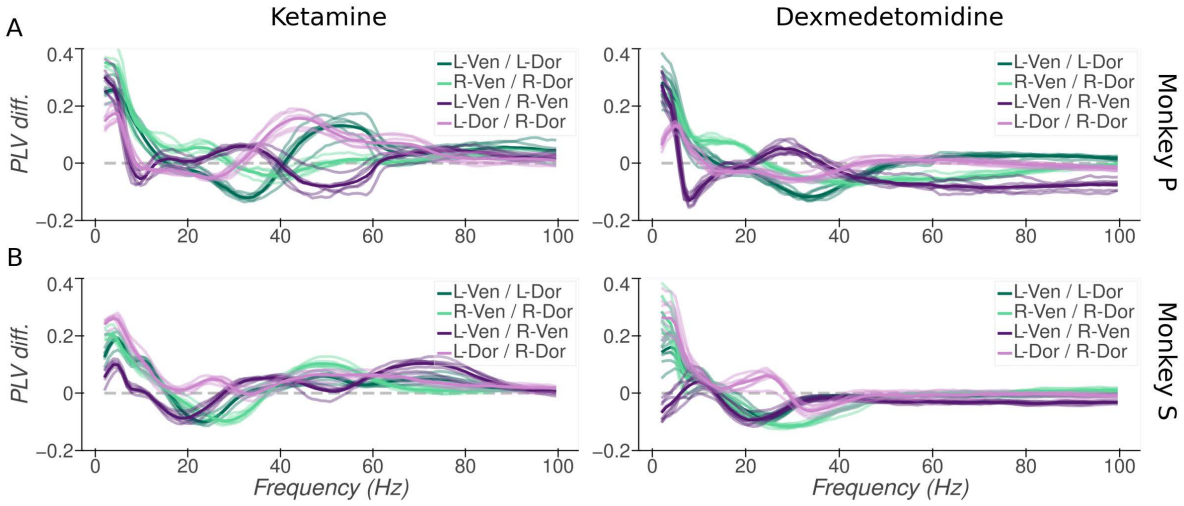

Figure S2: Changes in phase locking were consistent across monkeys, sessions. Difference in PLV (during – before anesthetics) for two monkeys (A) Monkey P and (B) Monkey S. Each line indicates one session; the darker line is the average across all sessions.

Fig. S3

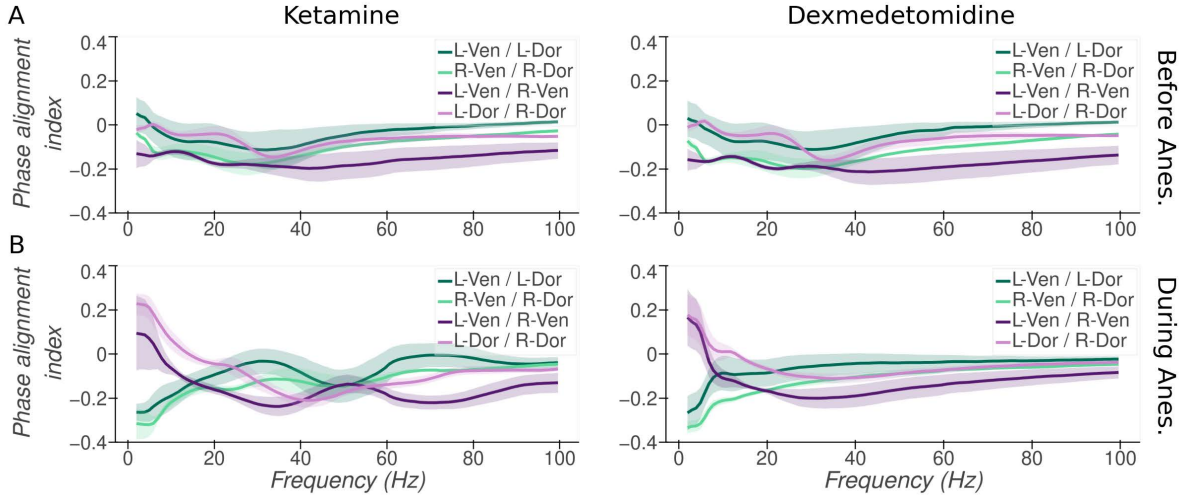

Figure S3: Phase alignment shifted with anesthetics. Phase alignment index cos(Δϕ) (A) before anesthetics, and (B) during anesthetics (shading shows 99% confidence intervals across sessions). Difference between (A) and (B) shown in Figure 3C.

Fig. S4

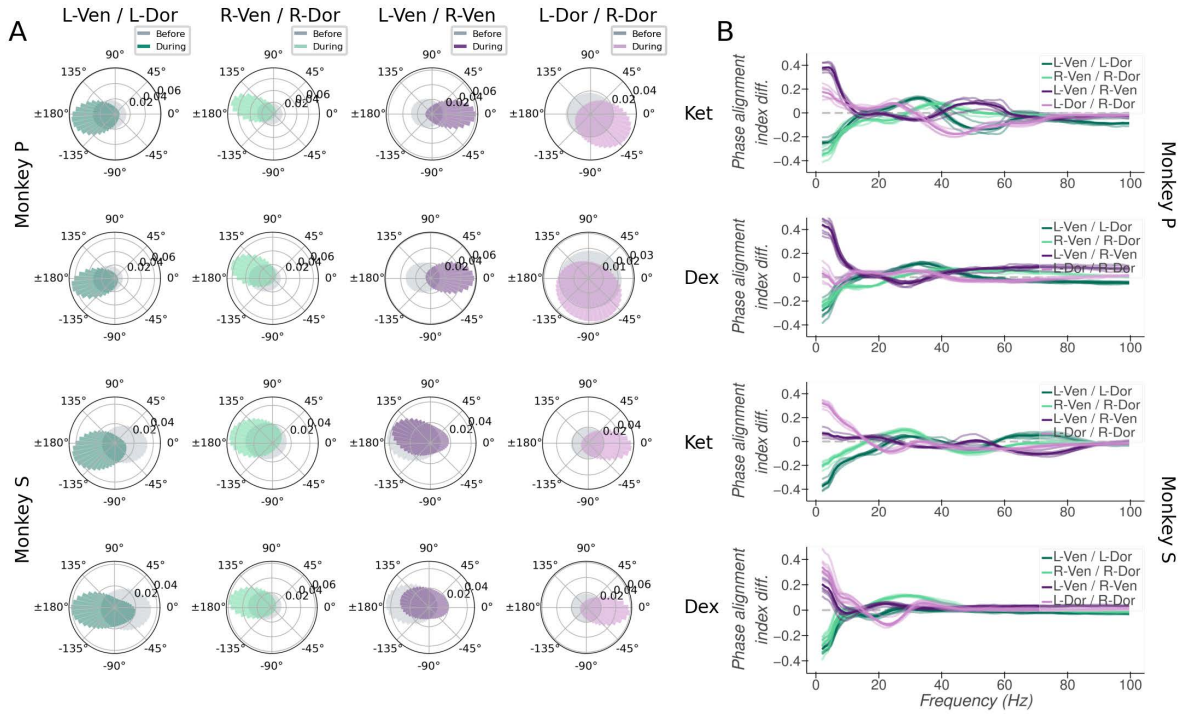

Figure S4: Shift in phase alignment was consistent across monkeys, sessions. (A) Histograms of phase offsets in the 1-4 Hz range between indicated regions for each drug, split by monkey (top two rows are Monkey P, bottom two rows are Monkey S). (B) Changes in phase alignment index for each drug and monkey (corresponding to rows in A). Each line indicates one session; the darker line is the average across all sessions.

Fig. S5

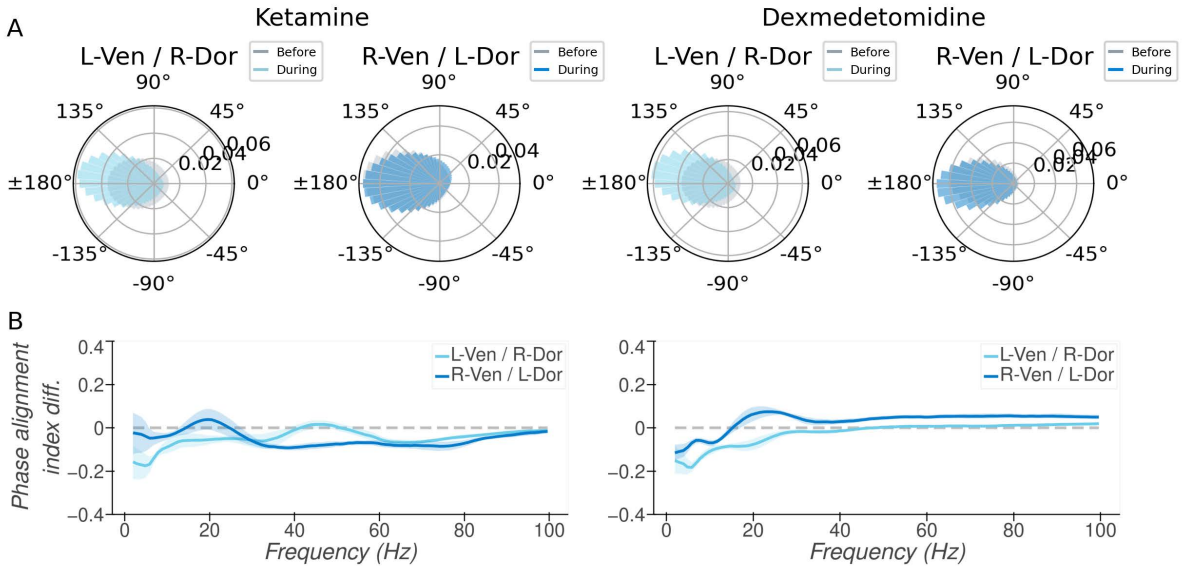

Figure S5: Phase alignment decreased slightly between diagonal regions. (A) Phase offsets of cross-hemisphere / cross-region pairs. (B) Changes in cross-hemisphere / cross-region phase alignment index (shading shows 99% confidence intervals across sessions).