Primary motor and sensory cortical areas communicate via spatiotemporally coordinated networks at multiple frequencies

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Skilled movements rely on sensory information to shape optimal motor responses, for which the sensory and motor cortical areas are critical. How these areas interact to mediate sensorimotor integration is largely unknown. Here, we measure intercortical coherence between the orofacial motor (MIO) and somatosensory (SIo) areas of cortex as monkeys learn to generate tongue-protrusive force. We report that coherence between MIO and SIo is reciprocal and that neuroplastic changes in coherence gradually emerge over a few days. These functional networks of coherent spiking and local field potentials exhibit frequency-specific spatiotemporal properties. During force generation, theta coherence (2–6 Hz) is prominent and exhibited by numerous paired signals; before or after force generation, coherence is evident in alpha (6–13 Hz), beta (15–30 Hz), and gamma (30–50 Hz) bands, but the functional networks are smaller and weaker. Unlike coherence in the higher frequency bands, the distribution of the phase at peak theta coherence is bimodal with peaks near 0° and ±180°, suggesting that communication between somatosensory and motor areas is coordinated temporally by the phase of theta coherence. Time-sensitive sensorimotor integration and plasticity may rely on coherence of local and large-scale functional networks for cortical processes to operate at multiple temporal and spatial scales.

Results

We trained two naïve monkeys to protrude the tongue onto a force transducer and apply isometric force at the level cued by target positions shown on a video screen (Fig. 1A). The monkeys learned to associate the target position with the required tongue-protrusive force after a few hundred trials, but proficient task performance was achieved after 8–12 training days (Fig. 1B and C). To investigate the emergence of interactions between MIO and SIo as monkeys learned to associate sensory information with motor response, we evaluated the coherence between the spiking of neurons recorded in MIO and SIo (MS in Fig. 2A) and the coherence between the spiking of MIO or SIo neurons with LFPs in SIo or MIO, respectively (MSf and SMf in Fig. 2B) These measures of coherence are presumed to represent the correlation of the outputs from both areas (MS) and the correlation of the outputs from one area with the inputs in the other (MSf and SMf). For each of the 5 sampled training days, D1–D5, we estimated coherence by using a 0.5-s sliding window with 0.01-s steps to show a time-resolved coherence profile in the theta (2–6 Hz), alpha (6–13 Hz), beta (15–30 Hz), and gamma (30–50 Hz) bands. Coherence in these frequency bands is believed to play a role in attention, memory, motor control, and plasticity (16, 18–20).

Significance

Sensorimotor integration is important for the acquisition and performance of motor skills. Here, we show the emergence of neuroplastic changes in the interactions between the motor and somatosensory areas of the primate cortex during learning. Interareal coherence is frequency- and network-specific and exhibits a spatiotemporal organization. Time-sensitive sensorimotor integration and plasticity may rely on coherence of local and large-scale sensorimotor networks in order for cortical processes to operate at multiple temporal and spatial scales. Understanding cortico-cortical interactions may be important for developing therapies for sensorimotor disorders, such as those affecting feeding and speech that are commonly found in stroke and Parkinson's disease.

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the results for alpha/beta were similar to gamma, we only discuss the results in the gamma band here and show the results for alpha and beta bands in Supporting Information.

**Frequency-Specific Modulation of Spike–Spike Coherence (MS) During Task Performance.** Coherence between the spiking of MIo and Slo neurons (MS) at multiple frequencies was dynamically modulated; single neuronal pairs exhibited increases and decreases in coherence as well as firing-rate modulations relative to the onset of tongue-protrusive force (Fig. 2B and C, and Fig. S1). Similar patterns were observed for the MS coherence across neuronal pairs with significant modulation of coherence (Fig. 2D, shuffle test, $P < 0.01$), consistent with the task modulation of theta coherence previously found within MIo and within Slo (16). Out of all of the possible combinations of paired signals ($n = 44,152$) from 10 datasets, the proportion of neuronal pairs that showed significant task modulation of MS coherence (i.e., “functional network”) was highest in theta and was significantly lower in the higher frequency bands (Fig. S1E, McNemar test, $P < 0.01$). The larger theta network (i.e., highest proportion of paired neurons with significant coherence) exhibited the strongest coherence (i.e., highest mean peak coherence), whereas the sparser networks in the alpha/beta/gamma bands exhibited weaker coherence. This was observed for each monkey (Fig. 2E) and for data pooled across monkeys [Kruskal–Wallis peak by frequency, $x^2_{(3,2032)} = 10,683$, $P = 0$, post hoc, $P < 0.001$]. Differences in spectral power across frequencies cannot explain this result as the cross-spectrum is normalized by the autospectra. We also found frequency-specific differences in the time of peak MS coherence; pairs of MIo and Slo neurons exhibited a unimodal distribution of time of peak coherence in theta and a bimodal distribution in all other frequency bands [Fig. 2F, Kruskal–Wallis peak times by frequency, $x^2_{(3,2032)} = 122$, $P = 3e-26$]. The mean time to peak theta coherence (0.03 s, SD = 0.07) occurred before and at force onset (note that coherence values were aligned to the right edge of the 0.5-s window). This suggests that theta coherence may play a role in generating the tongue-protrusive force. In contrast, the distribution of the times of peak gamma coherence was bimodal based on a two-component Gaussian mixture model having the lowest Akaike information criterion compared with models with one, three, or four components. The bimodal distribution of the peak times of gamma coherence was further confirmed by extending the time windows analyzed relative to force onset (Fig. 2F, Inset, and Fig. S2), indicating a suppression of gamma coherence at force onset. Peaks

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**Fig. 1.** Behavioral task and performance. (A) Diagram of the sequence of events in a trial of the tongue protrusion task. The blue square represents the force cursor, whereas the red and green boxes represent the base and force targets. (B) Success rates shown separately for each monkey. Dots mark the 5 d that were analyzed (i.e., sampled training days D1 to D5). Shaded area corresponds to training days when the required force level was 50 g. Required force level was increased to 80 g when success rates reached >75% for at least 3 consecutive days. (C) Reaction time shown as mean ($\pm$1 SEM error bars) across all trials for D1 to D5. B and C adapted from ref. 16.

**Fig. 2.** Frequency-specific modulation of MS coherence between MIo and Slo neurons. (A) Schema of paired signals used in interareal coherence: paired spikes from MIo and Slo (MS), paired MIo spikes and Slo LFPs (MS), and paired Slo spikes and MIo LFPs (SM). We also analyzed intraareal coherence, i.e., paired spikes and LFPs within each area (MMf and SSf). (B) Coherogram of two pairs of neurons with significant MS coherence (color scale). Coherence is aligned to the right edge of the 0.5-s window, e.g., coherence at force onset (FO) corresponds to a 0.5-s window ending at FO. Mean firing rates of MIo and Slo neurons whose coherent activity is shown in B. Rates were calculated using a 0.5-s sliding window with 0.01-s steps per trial then averaged across trials. Gray shades denote 1 SEM. Orange line denotes mean tongue-protrusive force of the first 100 trials of a training day. The force profile is averaged over a 0.5-s window. Timescales for rates and force are plotted to the right edge of 0.5-s window over which they were computed. (D) Mean coherence across all unique pairs of neurons (SI Methods) with significant coherence in one dataset, shown for the theta-alpha bands ($n = 75$ pairs) and beta-gamma bands ($n = 67$), respectively. (E) Histogram of peak coherence of all pairs with significant coherence in the theta and gamma bands. Shown for monkeys Y ($\mu_{\text{theta}} = 8.148$, $\sigma_{\text{theta}} = 967$) and B ($\mu_{\text{beta}} = 2.874$, $\sigma_{\text{beta}} = 271$) separately. Data pooled across D1 to D5. M, mean. (F) As in E, for data of peak coherence. (Inset) Histogram of time of peak gamma coherence ranging from −1.5 and 1 s relative to FO. Green line indicates Gaussian mixture model fit using two components. Data include only unique neuronal pairs with significant modulation of coherence, pooled across days and monkeys.
Changes in Spike–Spike Coherence (MS) with Learning. Fig. 3 A and B illustrates the coherent activity of the population of paired MIo–Slo neurons for D1 and D5 of monkey Y. Proportions of neuronal pairs with significant modulation of MS coherence changed during training from day to day. We tested statistical significance between D1 and D5 for each band and found P < 0.05 (Fig. 3C, binomial test). We also found day-to-day changes in peak and time of peak coherence in the theta band (Fig. 3D and Fig. S6, Kruskal–Wallis, peak by days: x(4,1107)2 = 53, P = 7e-11; peak time by days: x(4,1107)2 = 32, P = 2e-6) but not in the other frequency bands (Kruskal–Wallis, P > 0.10, peak/time of peak coherence by days separately for alpha/beta/gamma). We did not find any systematic changes in peak and time of peak coherence in relation to changes in tongue protrusion force, success rates, and reaction and movement times (Fig. S7, Pearson’s correlation, P > 0.10). Furthermore, changes in firing rates cannot account for changes in MS coherence; no significant correlation was found between mean firing rates and mean MS coherence (Fig. S8, Pearson’s correlation, P > 0.10). These indicate that coherence does not directly relate to the encoding of specific behavioral parameters and suggests a role of coherence in the spatiotemporal coordination of different functional networks that emerge or are reshaped during learning.

Network-Specific Modulation of Spike–Field Coherence. LFPs are considered to represent the aggregate subthreshold activity of neurons in a localized area near the recording electrode (21, 22), thereby providing information about the inputs to an area. A brief description of LFP properties in the orofacial sensorimotor cortex relevant to our analyses is presented in the SI Results and Figs. S9 and S10. Interareal spike–field coherence (MSf and SMf) also exhibited task modulation across multiple frequencies as illustrated for single pairs and for the population of paired signals (Fig. 4A and B, and Fig. S11). The task modulation of MSf and SMf coherence was distinct from the modulation of LFP spectral power in MIo and Slo (Fig. S10). As was found in MS coherence, the spike–field coherent networks were large and strong in theta and were sparse and weak in alpha/beta/gamma [Fig. S12; McNemar test, P < 0.01; Kruskal–Wallis, peak by
frequency, MSf: \( x^2_{(3,18983)} = 3558, P = 0; \) SMf: \( x^2_{(2,18983)} = 2187, P = 0, \) post hoc, \( P < 0.01 \). Spike–field networks also exhibited preferred frequency bands; MSf coherence was stronger than SMf in theta, whereas SMf coherence was stronger than MSf in gamma [Kruskal–Wallis, peak by networks, theta: \( x^2_{(2,64170)} = 70, P = 5e-15 \); post hoc, \( P < 0.001 \)]. Theoretical work has suggested that higher firing rates are correlated with stronger spike–field coherence (23). However, differences in firing rates of neurons cannot account for these results as no linear relations were found between firing rates of MIo or SIo neurons and the MSf/SMf coherence in either theta or gamma bands (Fig. S13). Temporal differences between theta and gamma also support the notion of frequency-specific roles of coherence in MIo and SIo. In theta MSf and SMf, the distributions of time of peak coherence were unimodal with peaks around force onset but the distributions were bimodal in gamma with peaks around ±0.35 s relative to force onset (Fig. 4C and Table S1).

**Bimodal Distribution of Phase at Peak Coherence Reveals Subnetworks.** The coherence analyses also measure the phase difference, \( \phi \), between two signals \( x \) and \( y \). Two signals are in-phase when \( \phi(x, y) = 0^\circ \), or antiphase when \( \phi(x, y) = \pm 180^\circ \). The phase at peak coherence (\( \phi \)) may provide important information on the temporal organization of the coherent signals. For MS coherence, the distribution of \( \phi \) was bimodal in theta (Fig. 5A, blue, Rayleigh test for bimodal distribution, \( P < 0.00001; \) circular mean: \(-2^\circ \) and \( 178^\circ \)) but uniform in gamma (Fig. 5A, fuchsia, Rayleigh test, \( P > 0.10 \)). The bimodal distribution of theta C\( \phi \) could not be explained by paired neurons that modulated their firing rate in phase (i.e., both neurons increased or decreased their firing rate concurrently) or out of phase (i.e., one increased its firing rate while the other decreased its firing rate) with each other relative to force generation (SI Results, Fig. S14). A similar bimodal distribution of theta C\( \phi \) was observed in MSf and SMf (Fig. 5B, blue; Rayleigh test for bimodal distribution, \( P < 0.00001 \); circular mean: MSf: \(-4^\circ \) and \( 176^\circ \); SMf: \(-6^\circ \) and \( 174^\circ \) at 6 Hz), but the gamma C\( \phi \) distribution in MSf and SMf was unimodal (Fig. 5B, fuchsia, Rayleigh test for unimodal distribution, \( P < 0.00001 \); circular mean: MSf: \(-31^\circ \); SMf: \(-26^\circ \) at 40 Hz). The bimodal distribution of theta C\( \phi \) was also found in the intraareal coherence MMf and SSf (Rayleigh test for bimodal distribution, \( P < 0.00001 \)). These results suggest two subnetworks of coherent signals, i.e., in-phase and antiphase. Thus, we examined the theta C\( \phi \) distribution of each neuron with all other neurons in MS to see whether there were distinct subpopulations of neurons. We found that, in MS, a larger number of neurons exhibited a significant bimodal theta C\( \phi \) distribution (Rayleigh test for bimodal distribution, \( P < 0.05 \); mean and SEM across D1–D5; Y: \( 61 \pm 13\% \); B: \( 40 \pm 9\% \)) than unimodal distribution (Rayleigh test for unimodal distribution, \( P < 0.05 \); Y: \( 7 \pm 2\% \); B: \( 4 \pm 1\% \)). We found the reverse for MSf and SMf; over 50\% of single neurons in MIo and SIo exhibited a single preferred C\( \phi \) relation with all theta oscillations in MSf and SMf, respectively (Fig. 5C, top plots; Rayleigh test for unimodal distribution, \( P < 0.05 \)), whereas a smaller number of single
neurons showed two preferred Cϕ (Fig. 5C, bottom plots; Y: MSf, 17 ± 5%; SMf, 13 ± 3%; B: MSf, 21 ± 6%; SMf, 19 ± 5%). We verified that phase lags did not depend on specific LFP channels because Cϕ distributions of each LFP channel with all single units were also bimodal (0° and 180°). Last, we examined the temporal organization based on the Cϕ by comparing the time of peak coherence of paired signals whose Cϕ fell between −30° to 30° (i.e., the in-phase subnetwork) and between −150° to 150° (i.e., the antiphase subnetwork). In MS, time of peak coherence of the in-phase neurons was significantly earlier than that of the anti-phase neurons (Fig. 5D, red; Mann–Whitney, P < 0.001). However, in both SMf and MSf, the antiphase subnetwork had significantly earlier time of peak coherence than the in-phase subnetwork (Fig. 5D, brown and black; P < 0.001). Time of peak coherence of both in-phase and antiphase subnetworks in SMf were significantly earlier than in MSf (Fig. 5D, green and orange; P < 0.001). These results indicate temporal differences based on Cϕ and the network: in-phase MS (n = 4,046) → antiphase SMf (n = 3,842) → antiphase MSf (n = 2,873) → antiphase MS (n = 2,895) and in-phase SMf (n = 2,229) → in-phase MSf (n = 3,217).

**Coherent Activity Follows a Spatiotemporal Pattern.** Fig. 3 A and B shows that coherent neuronal pairs do not reach their peak activity all at the same time. Does the spatial location of coherent neurons influence the timing and the magnitude of their peak coherence? We tested this in MS, MSf, and SMF for both theta and gamma coherence but only found significant results in theta (SI Results, Table S2, and Fig. S15). Fig. 6 A4 maps the medio-lateral progression of the time of peak theta MSf coherence on the MIO array from D3 of monkey Y; the spatial gradient was apparent from 0.3 s before force onset when MIO neurons located medially exhibited the earliest peak MSF coherence. At 0.4 s after force onset, MIO neurons that exhibited peak coherence were mostly at the lateral border. The mean (across training days) spatial gradient for time of peak theta coherence for MIO neurons in MS and MSf was initiated close to the central sulcus and progressed in the rostrolateral direction (Fig. 6 B and C, MIO array). This may be related to our previous finding that MIO neurons whose spiking activity led the tongue-protrusive force were located closer to the central sulcus than neurons whose spiking activity lagged the force (16). For SLO neurons in MS and SMF, the mean spatial gradient for time of peak theta coherence was from medial to lateral (Fig. 6 C, SLO array). Because opening of the lips preceded tongue protrusion, the spatial gradient of the time of peak coherence may relate to the order in which sensory information was received from the lips and the tongue. Indeed, mechanoreceptive fields (RFs) of the lips are located at the medial border of SLO and RFs of the tongue at the lateral border of SLO (24). For the LFP component of MS and SMF, time of peak coherence progressed medially and toward the central sulcus for MSF and medially for SIF (Fig. S1A4, dashed arrows). The results suggest a spatiotemporal organization of coherence based on the temporal relation of MIO neurons’ spiking to tongue force and on the spatial features of MIO and SLO neurons’ RFs.

**Discussion**

To our knowledge, this study provides the first documentation of the emergence of neuropsychiatric changes in the coherence between motor and somatosensory areas of the primate cortex during sensorimotor learning. Interareal coherence was frequency- and network-specific and exhibited a spatiotemporal organization. Such interactions may imply communication between sensory and motor cortical areas for integrating new sensory and motor events and for forming and retrieving memories during learning.

**Coherent Networks Involve Multiple Frequencies.** The simultaneous presence of cortical rhythms in multiple frequencies in the arm sensorimotor cortex has been reported (25, 26), but (to our knowledge) this is the first documentation of frequency-specific coherent activity in the orofacial sensorimotor cortex. Larger and stronger sensorimotor networks occurred in theta, whereas sparser and weaker networks occurred in alpha/beta/gamma, consistent with the general feature of cortical rhythms that slow oscillations engage larger networks whereas fast oscillations engage more localized networks (27). Synchronous activity of local- and large-scale networks may be organized through multiple frequency bands for different cortical processes to operate at multiple temporal and spatial scales. Specifically, different functional demands at different phases of the task may require interareal coherence at different frequencies. Previous studies in the arm sensorimotor cortex suggest that theta synchrony is organized according to movement phases (28, 29). Thus, the high theta coherence at force onset may relate to the generation of tongue-protrusive force. In contrast, the high gamma coherence before and after force onset may relate to other processes such as sensory gating (30, 31), attention (18), and memory encoding/retrieval in association with theta coherence (32).

**Reciprocal Interaction Between MIO and SLO.** The observed interactions between MIO and SLO may be explained by a common source of modulatory activity, such as from the thalamus and not due to direct cortico-cortical communication. There are abundant projections from thalamus to MIO and SLO (11, 33), and thalamic neurons have been found to oscillate at 6, 10, and 40 Hz and thus have the potential to generate an oscillatory drive to the cortex in these frequencies (22, 34, 35). However, oscillations may be initiated in the cortex and propagated to the thalamus, which then sends oscillations back to the cortex, thus increasing the cortico-thalamo-cortical resonance (36). This is in agreement with findings in rats, which have spike-and-wave discharges originating from SLO, and then propagating to the thalamus (37). Alternatively, our results may instead represent a direct interaction between MIO and SLO. The dense anatomical connections between MIO and SLO provide a substrate for coherent firing of neurons that may underlie the formation of neuronal assemblies (2, 38, 39). Thus, the increased proportion of coherent neurons may represent the new coupling of a motor output to specific sensory inputs as learning unfolds. Our results also suggest that this process involves reciprocal interactions; MIO modulates sensory processing in SLO (40, 41) and SLO transmits afferent information to MIO critical for successful task performance (5, 6, 42, 43). Because both MIO and SLO have bilateral orofacial representations, cross-hemisphere interactions in the orofacial sensorimotor area may share some properties of the intercortical coherence observed here.

**Coherence Phase Reveals Temporal Organization of Subnetworks.** To our knowledge, this study is the first to report a bimodal distribution of phase at peak theta coherence in the sensorimotor cortex, i.e., in-phase (zero lag) and antiphase (near 180° lag). Zero-lag coherence has been suggested to result from either common input, reciprocal interaction, or a combination of both (44), whereas non-zero-lag coherence in gamma has been suggested to reflect interareal conduction delays in unidirectional interactions (45–47). Antiphase synchronization (15–30 Hz) between spikes in the parietal reach region and LFPs in the dorsal premotor cortex has been implicated in down-modulation of communication to selectively prevent transmission of movement-related information (48). Likewise, bimodal distributions of relative phases (0° and 180°) between LFPs (8–25 Hz) in the prefrontal and posterior parietal cortical areas has been suggested to represent specific patterns of coupling among neurons in these areas (49). Given that conduction delays within an area and even across areas are much smaller than the half period of a theta cycle, the antiphase relations in theta coherence found here are likely not due to conduction delays but may represent different populations of MIO neurons whose activity leads or lags the force generation (16, 49) or a down-modulation of communication between MIO and SLO to prevent transmission of irrelevant sensory or movement-related information (48). The results further refine the understanding of the temporal sequence of coherent activity between MIO and SLO and suggest that cortico-cortical...
coherence may use phase to organize the activity of neuronal ensembles at different timescales or for segregating feedforward and feedback influences so that orofacial sensorimotor behaviors using different muscles and motor patterns are appropriately coordinated during learning.

Methods

Subjects. All experiments were performed in two adult male rhesus macaques (Macaca mulatta), B (10 kg) and Y (12 kg). All protocols were approved by the University of Chicago Animal Care and Use Committee and complied with the National Institutes of Health Guide for the Care and Use of Laboratory Animals (50).

Behavioral Task. We used a long-term learning paradigm wherein the subjects were exposed to the same behavioral task parameters over days until subjects achieve a success rate >75% consistently for 3 d (16). Monkeys were trained to protrude the tongue onto a force transducer and apply isometric force at the level cued by target positions. Fig. 1A illustrates the sequence of events in a trial. Detailed description of the task can be found in SI Methods. The behavioral program was written using Spike2 software (Cambridge Electronic Design). Force transduction (Research Transducers; model 4602-D-03) and digital signals and the behavioral event logs and time stamps were recorded at 2 kHz and stored using a Power 1401 data acquisition system (Cambridge Electronic Design). User-designed pulse signals were generated to mark behavioral events and were sent to the neural data acquisition systems for offline synchronization of time stamps across the different data acquisition systems. Further details are available in SI Methods.

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