Frequency-specific mechanism links human brain networks for spatial attention

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Selective attention allows us to filter out irrelevant information in the environment and focus neural resources on information relevant to our current goals. Functional brain-imaging studies have identified networks of broadly distributed brain regions that are recruited during different attention processes; however, the dynamics by which these networks enable selection are not well understood. Here, we first used functional MRI to localize dorsal and ventral attention networks in human epileptic subjects undergoing seizure monitoring. We subsequently recorded cortical physiology using subdural electrocorticography during a spatial-attention task to study network dynamics. Attention networks become selectively phase-modulated at low frequencies (δ , θ) during the same task epochs in which they are recruited in functional MRI. This mechanism may alter the excitability of task-relevant regions or their effective connectivity. Furthermore, different attention processes (holding vs. shifting attention) are associated with synchrony at different frequencies, which may minimize unnecessary cross-talk between separate neuronal processes.

One of the hallmarks of effective behavior is the ability to flexibly attend to particular stimuli in the environment. Selective attention can be driven endogenously by one's current goals or by salient external stimuli. Human neuroimaging studies have identified two sets of fronto-parietal regions that are recruited during these two types of attention. A set of dorsal fronto-parietal regions (dorsal attention network or DAN) shows sustained activity during endogenous or goal-driven attention (1), and reorienting to unexpected targets transiently activates both the DAN and a second set of regions, the ventral attention network (VAN) (2). Although functional MRI (fMRI) has identified the brain regions that are involved in these attentional operations (3, 4), the slow nature of the hemodynamic response has severely limited the study of network dynamics at behaviorally relevant time scales (5). Here, we report results obtained by cortical surface (electrocorticography or ECoG) recordings in epilepsy patients undergoing clinical monitoring to identify seizure foci. Electrode locations for each subject were colocalized with functional brain networks, including the DAN and VAN identified in the same subjects using fMRI. This experimental paradigm allowed us to objectively link fast electrophysiological dynamics, during performance of an attention task, to well-studied functional brain networks.

ECoG measures nonspiking, local field potential oscillations across a range of frequencies, which are thought to reflect fluctuations in local neuronal excitability (6, 7). Phase modulations of activity within a region and between regions may therefore affect, respectively, their ability to respond to inputs and to transfer information between one another (8, 9). In support of this theory, previous studies in both animals and humans have shown that either local or long-distance synchrony change in a task-specific manner; for example with visual attention, sensory-motor integration, or working memory (10–17).

In this study, we examine whether task-specific modulations of synchrony occur during a well-characterized spatial attention (Posner) task in both task-relevant (DAN, VAN, sensory-motor)

and irrelevant (default-mode) networks previously identified with fMRI. We predicted that attending to a spatially cued location or reorienting to the location of an unexpected target would produce selective phase modulations within and synchronization within and between task-relevant but not task-irrelevant networks based on fMRI.

Results

Posner Spatial Orienting Task. Seven invasively monitored patients performed a version of the Posner spatial cueing task, a standard paradigm for studying attention to spatial locations. Subjects were cued with a central arrow (500 ms) to attend to the side of the monitor where an upcoming target was likely to appear. After a brief (500 ms) delay, a rotated “L” or “T” was presented peripherally on the cued side (80% of trials, “valid”), or the uncued side (20% of trials, “invalid”) of the monitor. Subjects were asked to respond as quickly and accurately as possible with one of two mouse buttons to indicate the target identity (Fig. 1). On average, subjects performed the task with 90.1% accuracy. One outlier subject only responded correctly 75.6% of the time, so we eliminated this subject's data from subsequent analyses. The remaining six subjects responded with 92.5% accuracy on average (range: 85.8–97.2%), and all of them responded faster to valid than invalid targets (paired *t* test, *P* < 0.05, across subjects). Subject-specific behavioral results are presented in [Tables S1 and S2](#).

Significance

Humans have the remarkable ability to flexibly attend to stimuli in the environment and seamlessly shift behaviors, depending on sensory conditions and internal goals. Neuroimaging studies have shown that tasks involving particular cognitive domains consistently recruit specific broadly distributed functional brain networks. A fundamental question in neuroscience is how the brain flexibly manages communication within and between these brain networks, allowing task-relevant regions to interact while minimizing the influence of task-irrelevant activity. In this report we show that low-frequency neuronal oscillations, which reflect fluctuations in neuronal excitability, are modulated selectively within task-relevant, but not irrelevant brain networks. This modulation of oscillatory activity may coordinate the selective routing of neuronal information within the brain during everyday behavior.

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Fig. 6. Phase-clustering within and between task-relevant and -irrelevant networks. (A) Faded lines represent average phases across trials of individual electrodes, weighted by each electrode's ITC at that frequency and time point, from electrodes over the DAN, SMN, and DMN in a single patient at 2 Hz, at a time point during the delay period. Dark lines represent the interelectrode average. The angle of the resultant vector is the average phase across the group of electrodes and the magnitude relates to the degree of clustering between the electrodes. Note that the 2-Hz phases at DAN and SMN electrodes are much more tightly clustered than the phases at DMN electrodes. (B) Differences between the average DAN and average SMN phases, for the same subject and time point considered in A. (C) Phase difference between average DAN and average SMN phases, over the time course of a trial.

phase-locked activity may arise either because of an external stimulus or an endogenous source. ITC can also reflect either an additive signal superimposed on ongoing oscillations or phase-resetting of the ongoing oscillations themselves. Here, we not only showed that task-relevant brain regions became simultaneously phase-modulated (Figs. 2–4), but that they became more in phase with each other during the task (Fig. 6). More direct evidence for task-dependent synchronization between task-relevant regions comes from the analysis of PLV, which reflects the phase consistency between regions over time. Consistent with the ITC results, we showed that electrodes over task-relevant networks became more phase-locked with each other during the Posner task trial, relative to the ITI (Fig. 5). Task-irrelevant electrodes/networks (e.g., in the DMN), on the other hand, showed weak to no phase modulation during the task. We suggest that the observed network-specific phase modulations reflect enhanced excitability at or effective connectivity between task-relevant brain regions.

The spatial selectivity of phase-resetting in DAN and visual regions that contain topographic maps (25–27) also suggests that phase modulations may be important not only for linking different regions of a network, but also for selecting specific neuronal populations (e.g., neurons coding for left vs. right locations) within a network.

Although our surface recordings are unable to determine underlying brain structures that may bring about this synchrony, other anatomical studies, primarily in monkeys, suggest potential neural substrates. The pulvinar nucleus of the thalamus, for example, has broadly distributed cortical connections [most direct cortico-cortico connections have a parallel indirect path through the pulvinar (28)] and exhibits both attention-modulated spike rate (29) and synchrony with visual areas (30). The inhibitory thalamic reticular nucleus, which receives overlapping projections from prefrontal cortex and higher-order sensory cortical areas, may also play a role in modulating incoming sensory information with selective attention (15, 31, 32).

Frequency-Specific Phenomena with Two Types of Attention. One key aspect of our results is that phase modulations occurred in different frequency bands depending on the network and the

relevant task process (Figs. 2 and 4, and Fig. S6). Sustained δ -phase modulations were observed in the DAN, SMN, and visual areas during the cue and delay periods, while maintaining attention to the cued location and preparing for a motor response (Figs. 2 and 3). In contrast, transient phase resetting in the θ -band occurred in the DAN and VAN following invalid targets (Fig. 4B), when subjects reoriented attention to the unexpected target.

The δ -phase at stimulus onset has been shown to correlate both with the magnitude of a sensory response and reaction time to a stimulus (33), suggesting that δ -phase relates to the level of local neuronal excitability. The δ -oscillations can also entrain to the rhythm of a task when it is predictable, such that stimuli arrive at a particular oscillatory phase, for example that corresponding to maximum excitability (33). In our study, ITC during the delay peaked at 2 Hz (Fig. S6), which has a cycle of 500 ms, the exact duration of the delay period. In two subjects, who also performed a version of the Posner task with a variable delay between the cue and target, the δ ITC was not sustained during the delay period, as it was with a constant delay (Fig. S9). This result suggests that when the cue–target interval is fixed, δ -oscillations may phase-reset, such that target onset aligns with the phase of maximal excitability.

Previous work has shown that θ -phase modulates γ power (7, 34), and γ activity has been associated with active sensory processing (14, 35). Furthermore, stronger θ phase-reset with saccades during exploration of a stimulus has been associated with better subsequent recall of that stimulus (36). Thus, the θ phase-reset we observe following invalid targets may allow for optimal sensory processing of the unexpected stimulus.

We do not claim that the δ - and θ -frequencies at which phase modulations are observed in this paradigm are associated specifically with endogenous and stimulus-driven attention. Likely, the oscillations modulated by a task are determined by many factors, including the temporal structure of a task (33) and the distribution of brain regions recruited (37). However, the observation that phase-resetting occurred at multiple frequencies simultaneously, in some cases on the same electrode, suggests that synchrony across multiple frequencies is a potential mechanism to allow multiple neuronal processes to occur simultaneously without interference.

Although the main attention effects reported here are in the low-frequency δ - and θ -bands, several previous studies of visual attention have shown coherence at higher frequencies (β , γ) (14, 38–40). In some of these earlier studies, neurons were driven continuously with visual stimuli, and thus attention was not purely endogenous. These studies also had a randomized cue–target interval, making phase entrainment to the stimuli impossible, whereas our study had a fixed delay between the cue and target. Low-frequency oscillations have been shown to entrain to the rhythm of a task, when stimuli are presented in a rhythmic, predictable manner (33). On the other hand, γ synchrony, which enhances the efficacy of communication between regions (41), but which is more metabolically costly than low-frequency activity (42), may operate under conditions of temporal uncertainty (43). Notably, both the pulvinar and thalamic reticular nucleus, mentioned above as a potential generators of cortical synchronous activity, operate in both phasic (i.e., transient) and tonic (i.e., sustained) modes (29, 32). These two modes may underlie the low frequency [shown here (15)] versus sustained high-frequency coherence (14, 39) correlates of attention, respectively.

Conclusions

We emphasize three conclusions. First, phase-resetting as measured with ECoG was observed in electrodes involved in particular cognitive functions as predicted by neuroimaging. The striking correspondence between ECoG and blood-oxygen level-dependent signals measured with fMRI not only provides electrophysiological support for the distinction between dorsal

and ventral attention networks, but also validates our approach of using neuroimaging data to predict the functional properties of specific electrodes.

Second, our results support the view that modulations in low-frequency oscillatory activity during a task may alter the excitability at or effective connectivity between functionally relevant regions within and between networks. Increased ITC in task-relevant networks was accompanied by both an increase in phase-locking and a tighter clustering of phase values within and between task-relevant networks, consistent with enhanced communication among those regions.

Finally, task-related changes in synchronization were frequency-specific, in agreement with work showing that different frequency scales in the cortical physiology are associated with different cognitive processes or brain states (6, 44). The δ -frequency modulations were associated with endogenous maintenance of spatial attention in the DAN and SMN, whereas more transient shifts of attention involved θ -phase modulations in both the DAN and VAN. Frequency-specific synchronization may link neuronal populations at different temporal scales and allow simultaneous interactions between different sets of networks/brain regions without interference, as in amplitude modulation (AM) radio broadcasting, where signals from different stations are carried on radio waves of different frequencies.

Experimental Procedures

Subjects. Seven patients with drug-resistant epilepsy participated in this study; all were undergoing surgery at Barnes Jewish Hospital in St. Louis for seizure mapping via ECoG before resection of their epileptic foci. All subjects provided informed consent before participating, which had been reviewed and approved by the Washington University School of Medicine Institutional Review Board. Electrode locations were determined purely for clinical reasons and thus varied from patient to patient. Fig. S1B illustrates the approximate electrode locations for the patients who participated in this study.

General Methods. During the monitoring phase of this procedure, in which brain activity was recorded from the implanted electrodes, subjects performed a version of the Posner spatial cueing task, described earlier. We allowed at least 2 d for subjects to recover from the surgery/anesthesia before having them perform the task. Before the surgery to implant the electrodes, resting-state fMRI scans were obtained for each subject (to generate functional connectivity network maps), and were used to localize brain regions of interest for the ECoG analysis. Postoperative CT scans (with electrodes) were also obtained to enable coregistration of electrode coordinates with the fMRI data, unless otherwise noted otherwise in *SI Experimental Procedures*.

Detailed data analysis methods are included in *SI Experimental Procedures*.

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- Corbetta M, Shulman GL (2002) Control of goal-directed and stimulus-driven attention in the brain. *Nat Rev Neurosci* 3(3):201–215.
- Corbetta M, Patel G, Shulman GL (2008) The reorienting system of the human brain: From environment to theory of mind. *Neuron* 58(3):306–324.
- Kastner S, Pinsk MA, De Weerd P, Desimone R, Ungerleider LG (1999) Increased activity in human visual cortex during directed attention in the absence of visual stimulation. *Neuron* 22(4):751–761.
- Hopfinger JB, Buonocore MH, Mangun GR (2000) The neural mechanisms of top-down attentional control. *Nat Neurosci* 3(3):284–291.
- Logothetis NK (2008) What we can do and what we cannot do with fMRI. *Nature* 453(7197):869–878.
- Buzsáki G, Draguhn A (2004) Neuronal oscillations in cortical networks. *Science* 304(5679):1926–1929.
- Lakatos P, et al. (2005) An oscillatory hierarchy controlling neuronal excitability and stimulus processing in the auditory cortex. *J Neurophysiol* 94(3):1904–1911.
- Varela F, Lachaux JP, Rodriguez E, Martinerie J (2001) The brainweb: Phase synchronization and large-scale integration. *Nat Rev Neurosci* 2(4):229–239.
- Fries P (2005) A mechanism for cognitive dynamics: Neuronal communication through neuronal coherence. *Trends Cogn Sci* 9(10):474–480.
- Bressler SL, Coppola R, Nakamura R (1993) Episodic multiregional cortical coherence at multiple frequencies during visual task performance. *Nature* 366(6451):153–156.
- Sarnthein J, Petsche H, Rappelsberger P, Shaw GL, von Stein A (1998) Synchronization between prefrontal and posterior association cortex during human working memory. *Proc Natl Acad Sci USA* 95(12):7092–7096.
- Rodriguez E, et al. (1999) Perception's shadow: Long-distance synchronization of human brain activity. *Nature* 397(6718):430–433.
- von Stein A, Chiang C, König P (2000) Top-down processing mediated by interareal synchronization. *Proc Natl Acad Sci USA* 97(26):14748–14753.
- Fries P, Reynolds JH, Rorie AE, Desimone R (2001) Modulation of oscillatory neuronal synchronization by selective visual attention. *Science* 291(5508):1560–1563.
- Lakatos P, et al. (2009) The leading sense: Supramodal control of neurophysiological context by attention. *Neuron* 64(3):419–430.
- Siegel M, Donner TH, Oostenveld R, Fries P, Engel AK (2008) Neuronal synchronization along the dorsal visual pathway reflects the focus of spatial attention. *Neuron* 60(4):709–719.
- Saleh M, Reimer J, Penn R, Ojakangas CL, Hatsopoulos NG (2010) Fast and slow oscillations in human primary motor cortex predict oncoming behaviorally relevant cues. *Neuron* 65(4):461–471.
- Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL (2000) Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nat Neurosci* 3(3):292–297.
- Shulman GL, et al. (2003) Quantitative analysis of attention and detection signals during visual search. *J Neurophysiol* 90(5):3384–3397.
- Sylvester CM, Shulman GL, Jack AI, Corbetta M (2007) Asymmetry of anticipatory activity in visual cortex predicts the locus of attention and perception. *J Neurosci* 27(52):14424–14433.
- Sylvester CM, Shulman GL, Jack AI, Corbetta M (2009) Anticipatory and stimulus-evoked blood oxygenation level-dependent modulations related to spatial attention reflect a common additive signal. *J Neurosci* 29(34):10671–10682.
- Shulman GL, et al. (2010) Right hemisphere dominance during spatial selective attention and target detection occurs outside the dorsal frontoparietal network. *J Neurosci* 30(10):3640–3651.
- Buzsáki G (2006) *Rhythms of the Brain* (Oxford Univ Press, New York, NY).
- Desimone R, Duncan J (1995) Neural mechanisms of selective visual attention. *Annu Rev Neurosci* 18:193–222.
- DeYoe EA, et al. (1996) Mapping striate and extrastriate visual areas in human cerebral cortex. *Proc Natl Acad Sci USA* 93(6):2382–2386.
- Sereno MI, Pitzalis S, Martinez A (2001) Mapping of contralateral space in retinotopic coordinates by a parietal cortical area in humans. *Science* 294(5545):1350–1354.
- Silver MA, Kastner S (2009) Topographic maps in human frontal and parietal cortex. *Trends Cogn Sci* 13(11):488–495.
- Saalmann YB, Kastner S (2011) Cognitive and perceptual functions of the visual thalamus. *Neuron* 71(2):209–223.
- Petersen SE, Robinson DL, Keys W (1985) Pulvinar nuclei of the behaving rhesus monkey: Visual responses and their modulation. *J Neurophysiol* 54(4):867–886.
- Saalmann YB, Pinsk MA, Wang L, Li X, Kastner S (2012) The pulvinar regulates information transmission between cortical areas based on attention demands. *Science* 337(6095):753–756.
- Zikopoulos B, Barbas H (2006) Prefrontal projections to the thalamic reticular nucleus form a unique circuit for attentional mechanisms. *J Neurosci* 26(28):7348–7361.
- Zikopoulos B, Barbas H (2007) Circuits for multisensory integration and attentional modulation through the prefrontal cortex and the thalamic reticular nucleus in primates. *Rev Neurosci* 18(6):417–438.
- Lakatos P, Karmos G, Mehta AD, Uhlbert I, Schroeder CE (2008) Entrainment of neuronal oscillations as a mechanism of attentional selection. *Science* 320(5872):110–113.
- Canolty RT, et al. (2006) High gamma power is phase-locked to theta oscillations in human neocortex. *Science* 313(5793):1626–1628.
- Womelsdorf T, Fries P, Mitra PP, Desimone R (2006) Gamma-band synchronization in visual cortex predicts speed of change detection. *Nature* 439(7077):733–736.
- Jutras MJ, Fries P, Buffalo EA (2013) Oscillatory activity in the monkey hippocampus during visual exploration and memory formation. *Proc Natl Acad Sci USA* 110(32):13144–13149.
- von Stein A, Sarnthein J (2000) Different frequencies for different scales of cortical integration: From local gamma to long range alpha/theta synchronization. *Int J Psychophysiol* 38(3):301–313.
- Buschman TJ, Miller EK (2007) Top-down versus bottom-up control of attention in the prefrontal and posterior parietal cortices. *Science* 315(5820):1860–1862.
- Gregoriou GG, Gotts SJ, Zhou H, Desimone R (2009) Long-range neural coupling through synchronization with attention. *Prog Brain Res* 176:35–45.
- Saalmann YB, Pigarev IN, Vidyasagar TR (2007) Neural mechanisms of visual attention: How top-down feedback highlights relevant locations. *Science* 316(5831):1612–1615.
- Tallon-Baudry C (2009) The roles of gamma-band oscillatory synchrony in human visual cognition. *Front Biosci* 14:321–332.
- Schroeder CE, Lakatos P (2009) The gamma oscillation: Master or slave? *Brain Topogr* 22(1):24–26.
- Schroeder CE, Lakatos P (2009) Low-frequency neuronal oscillations as instruments of sensory selection. *Trends Neurosci* 32(1):9–18.
- Gaona CM, et al. (2011) Nonuniform high-gamma (60–500 Hz) power changes dissociate cognitive task and anatomy in human cortex. *J Neurosci* 31(6):2091–2100.