Theta modulation of inter-regional gamma synchronization during auditory attention control

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\textbf{ARTICLE INFO}

Article history:
Accepted 2 November 2011
Available online 7 November 2011

Keywords:
Theta
Gamma
Cross-frequency
EEG
Attention
Neural synchrony
Neural oscillation
Functional connectivity

\textbf{ABSTRACT}

Synchronization of gamma oscillations among brain regions is relevant for dynamically organizing communication among neurons to support cognitive and perceptual processing, including attention orienting. Recent research has demonstrated that inter-regional synchronization in the gamma-band is modulated by theta rhythms during cortical processing. It has been proposed that such cross-frequency dynamics underlie the integration of local processes into large-scale functional networks. To investigate the potential role of theta-gamma mechanisms during auditory attention control, we localized activated regions using EEG beamformer analysis, and calculated inter-regional gamma-band synchronization between activated regions as well as modulation of inter-regional gamma-band synchronization by the phase of cortical theta rhythms. Abundant synchronization of gamma-band oscillations among regions comprising the auditory attention control network was observed. This inter-regional gamma synchronization was modulated by theta phase. These results provide further evidence implicating inter-regional gamma-band synchronization, and theta-gamma interactions, in task-dependent communication among cortical regions, and provide the first evidence that such mechanisms are relevant for auditory attention control.

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\section{1. Introduction}

Converging lines of evidence from noninvasive electroencephalographic (EEG) and magnetoencephalographic (MEG) recordings in humans, as well as from implanted electrodes in animals, have implicated gamma-band phase synchronization between cortical regions in visual attention (Buschman and Miller, 2007; Doesburg et al. 2008; Gregoriou et al., 2009; Siegel et al., 2008). Synchronization among brain regions has been proposed as a mechanism mediating the dynamic assignment of functional connectivity to support enhanced processing of attended information (Fries, 2005). This interpretation is consistent with previous research linking gamma synchronization among brain regions to integrative network dynamics.
supporting the performance of a particular cognitive task (Sarnthein et al. 1998; Supp et al. 2007) or binding the features of an object (Doesburg et al. 2009a; Engel et al. 1991; Gray et al. 1989; Rodriguez et al. 1999; Rose and Büchel, 2005; Rose et al., 2006; Sarnthein et al. 1998). Changes in inter-regional gamma-band synchronization, computed from intracranial data collected from humans, have been observed during the performance of a cognitive task (Fell et al. 2006) and during changes in sleep state (Fell et al. 2003). The view that neuronal coherence is a mechanism for dynamically assigning functional connectivity in the brain also garners support from evidence linking inter-regional gamma-band synchronization to increased information exchange in the cortex (Womelsdorf et al. 2007).

Experimental evidence also indicates that modulation of cortical gamma rhythms by theta oscillations plays an important role in task-dependent cortical processing (Canolty et al., 2006; Demiralp et al. 2007; Jensen and Colgin, 2007; Sauseng et al. 2008; Schack et al. 2002). It has been proposed that gamma synchrony may relate to local integration, whereas theta rhythms pertain to long-distance functional coupling in the brain (von Stein and Sarnthein, 2000). Interplay among theta and gamma rhythms, moreover, has been purported to underpin organization of information in cortical circuits to support cognition (Ward 2003), and theta and gamma oscillations emerge from highly interrelated neurophysiological mechanisms that are critical for brain function (Llinás et al. 2005). From such a vista it would appear that coupling between theta and gamma oscillations is relevant for the integration of local neuronal processes into large-scale functional brain networks. This view is buttressed by findings that low frequency (3 Hz) modulation of inter-electrode gamma-band covariance has been associated with conscious recollection (Burgess and Ali, 2002), and that gamma-band phase locking between cortical regions during visual perception is modulated by the phase of cortical theta oscillations (Doesburg et al. 2009a).

Observations that inter-regional gamma-band synchronization is involved in attention control, and that gamma synchrony among brain regions is modulated by theta oscillations during cognitive processing, lead to the hypothesis that theta rhythms will modulate gamma-band synchronization between activated brain regions during attention control. To test this we seeded dipoles in regions identified as subtending auditory attention in space (shift-cue trials), or not to orient attention (neutral cue trials) (Fig. 1). Participants were faster to respond to target sounds on valid-cue trials (M=694 ms, SD=102 ms) than on either invalid-cue (M=716 ms, SD=106.8 ms) or neutral-cue (M=718 ms, SD=106.4 ms) trials. There was a main effect of cue type on reaction time (p=0.006) without any corresponding changes in discrimination accuracy (p=0.99), indicating that participants did shift attention to the cued location in preparation for the target. Thus, we may assume that during the cue-target interval on shift-cue trials participants were occupied in shifting attention from the fixation point to the appropriate side of the display in preparation for the upcoming target. See the original study by Störmer et al. 2009, where those results were initially published, for a more comprehensive behavioral analysis.

2. Results

2.1. Behavioral results

Participants performed an auditory attention task wherein on each trial they were instructed to orient their attention from the center fixation cross to the left or right side of auditory space (shift-cue trials), or not to orient attention (neutral cue trials) (Fig. 1). Participants were faster to respond to target sounds on valid-cue trials (M=694 ms, SD=102 ms) than on either invalid-cue (M=716 ms, SD=106.8 ms) or neutral-cue (M=718 ms, SD=106.4 ms) trials. There was a main effect of cue type on reaction time (p=0.006) without any corresponding changes in discrimination accuracy (p=0.99), indicating that participants did shift attention to the cued location in preparation for the target. Thus, we may assume that during the cue-target interval on shift-cue trials participants were occupied in shifting attention from the fixation point to the appropriate side of the display in preparation for the upcoming target. See the original study by Störmer et al. 2009, where those results were initially published, for a more comprehensive behavioral analysis.

2.2. Beamformer source localization

Beamformer source localization revealed statistically significant (p<0.01) bilateral activation of the superior temporal gyrus (STG), superior parietal lobe (SPL), inferior parietal lobe (IPL), and inferior frontal gyrus (IFG) during the cue-target interval for shift-cue trials, relative to neutral-cue trials. The Talairach coordinates (x, y, z) of cortical generators underlying auditory attention control were: STG:±55, −25, 12; SPL:±5, −55, 61; IPL:±48, −55, 34; IFG:±48, 38, 10. Locations of peaks of statistically significant activations are presented in Fig. 2. Additional detail regarding the results of the beamformer source localization is available in Green et al. 2011, where those findings were originally published.

2.3. Gamma-band inter-regional synchronization and activation

Auditory attention orienting was associated with significant task-dependent increases in inter-regional gamma-band synchronization between auditory cortex and parietal cortices (STG−SPL, STG−IPL), between activated parietal regions (SPL−IPL) and between frontal and parietal cortices (IPL−IFG; SPL−IFG). Gamma-band synchronization among brain regions was centered at various frequencies within the 30–50 Hz frequency range, depending on the source pair, and multiple instances of
statistically significant synchronization were observed for each source pair (Fig. 3). Consistent with the results of previous research, these task-dependent synchronizations were transient. In many instances multiple, successive, synchronizations were observed which appeared to follow a periodic time course consistent with a theta rate. No systematic changes in inter-regional synchrony were observed within the attention control network at frequencies outside the gamma-band. In addition to the gamma-band synchronization between cortical regions, increases in (local) gamma-band amplitude were also observed in the STG contralateral to the locus of auditory attention for both the right–neutral and left–neutral cue conditions (Fig. 4). For both conditions gamma-band activation was multiphasic, returning to baseline levels periodically for the right–neutral condition and dipping below baseline levels for the left–neutral cue condition.

2.4. Theta modulation of inter-regional gamma synchrony

Gamma-band synchrony among activated cortical regions was modulated by the phase of local theta oscillations (Fig. 5). The distribution of cross-frequency modulation within the auditory control network was complex, as statistically significant modulation was observed in both cerebral hemispheres for some source pairs, only observed in either the left or the right hemisphere for other source pairs, and not significantly modulated for other pairs. No systematic effects were seen when contrasting cross-frequency modulation across left and right cerebral hemispheres, or between shift–left and shift–right cue conditions, although differences for individual pairs were observed. For example, theta phase within IFG was demonstrated to modulate gamma-band synchrony among all source pairs, in at least one hemisphere, during the shift–left condition (STG–SPL, STG–IPL, IPL–SPL, IPL–IFG, SPL–IFG), whereas only SPL–IFG gamma synchrony within the right hemisphere was modulated by right IFG theta phase in the shift–right condition. Cross-frequency modulation was abundant, and included modulation of inter-regional synchronization by the phase of theta oscillations in a third region (i.e. gamma-band phase locking between STG and SPL modulated by theta phase in IFG). Inter-regional synchrony between source pairs was more commonly modulated by theta phase in one of the constituent regions, however, as 15 statistically significant results of this type were observed, compared with 10 statistically significant instances of modulation of synchrony by theta phase in a third region. The specific relations between theta phase and
gamma-band synchrony varied between source pairs and cue conditions. Fig. 6 depicts, for example, modulation of gamma-band phase locking between STG and SPL by the phase of theta rhythms within SPL. In this instance modulation patterns differed between left and right hemispheres, but not between shift-left and shift-right cue conditions. Both commonalities and differences were observed between the shift-left and shift-right conditions.

3. Discussion

We have demonstrated that inter-regional gamma-band phase synchronization is increased during auditory attention orienting within a distributed network of cortical regions activated during attention control. Furthermore, we have provided the first evidence that task-dependent inter-regional functional connectivity, as indexed by high-frequency oscillatory synchronization between discrete cortical regions, is modulated by the phase of cortical theta rhythms during attention orienting. These results add to a burgeoning body of evidence indicating that coupling between low- and high-frequency rhythms is an important feature of cortical network dynamics underlying large-scale transient functional connectivity supporting cognition (Burgess and Ali, 2002; Palva et al., 2005, 2010a, 2010b) and perception (Doesburg et al. 2009a). Reports of the co-activation and coupling of theta and gamma oscillations during cognitive processing have led to the view that cross-frequency coupling is critically relevant for neuronal processing (Canolty and Knight, 2010; Jensen and Colgin, 2007), as well as the proposal that these mechanisms form a central component of a neural code underlying hippocampal and cortical processing (Lisman and Buzsáki, 2008). Such an outlook also garners support from evidence that theta/gamma coupling is stronger in human cortex during cognitive activity, and that this enhancement of coupling is most pronounced in task-relevant cortical regions (Canolty et al. 2006). Aberrant increases in coupling between theta and gamma oscillations in cortex have been proposed to underlie the generation of positive symptoms across numerous neurological and neuropsychiatric conditions (Llinás et al. 1999), including disorders in the auditory domain such as tinnitus (De Ridder et al. 2011). Modulation of cortical gamma rhythms by theta oscillations seems to be of particular relevance for cognitive processes involving conscious recollection (Burgess and Ali, 2002) and conscious perception (Doesburg et al. 2009a). It is perhaps unsurprising, then, that theta modulation of gamma-band inter-regional synchronization is observed in endogenous attention orienting, a faculty closely aligned with conscious control.

Considerable evidence exists linking modulation of local cortical gamma oscillations to attentional processes (see Jensen et al., 2007 for review). Our observation of increased local gamma-band amplitude in auditory cortex contralateral to the locus of attention supports the view that local gamma oscillations are relevant for selective auditory attention. More recent evidence has demonstrated that long-range gamma-band synchronization is also relevant for visual attention (Buschman and Miller, 2007; Doesburg et al. 2008; Gregoriou et al., 2009; Siegel et al., 2008). The results of the present study convey additional support for this notion by demonstrating that task-dependent inter-regional gamma synchronization is relevant to auditory attention control. Moreover, our results indicate that oscillatory synchronization in the gamma-band is relevant for integration among diverse, distributed regions in the attention control network as we observed statistically significant synchronization between auditory and parietal cortical areas (STG–SPL; STG–IPL), among activated parietal regions (SPL–IPL) and between task-relevant regions of parietal and frontal cortex (SPL–IFG; IPL–IFG). Although elucidation of single-trial relations between inter-regional synchronization and performance is not possible in the present study, as PLVs are obtained by assessing the stability of phase relations across trials, previous research has established the relevance of gamma oscillations to performance in numerous cognitive contexts (see Riedar et al. 2011 for review) including selective attention (Siegel et al. 2008). By demonstrating task-dependent increases in inter-regional synchronization, relative to a neutral cue condition, we also confirmed that inter-regional synchronization is relevant to attention control, rather than simply to processing of the physical characteristics of the cue (where it also
probably plays a role). Understanding interactions among brain regions and oscillation frequencies during attention control is likely to enhance our understanding of the biological basis of disorders of attention, as inter-regional oscillatory coherence and cross-frequency interactions have been shown to be altered in children with attention deficit/hyperactivity disorder (Barry et al. 2011; Mazaheri et al. 2010).

Modulation of inter-regional gamma synchronization by theta oscillations may function to integrate local neural dynamics into large-scale task-dependent networks. Synchronization of specific constellations of cortical columns at a gamma rate has been related to the integration of selected neuronal elements into a functional ensemble (Engel et al. 1991; Gray et al. 1989); EEG evidence indicates that this principle also pertains to large scale dynamics in the central nervous system (Doesburg et al. 2009a; Rodriguez et al. 1999; Rose and Büchel, 2005; Rose et al., 2006; Supp et al. 2007). Recent research has demonstrated that thalamocortical interactions are relevant for the generation of cortical oscillations across a range of cognitively relevant frequencies including theta, alpha, beta and gamma rhythms (Hughes and Crunelli 2005; Hughes et al., 2009, Palva and Palva 2007). Task dependent changes in alpha power are thought to reflect inhibitory processing (Klimesch et al. 2007), whereas gamma oscillations are more closely linked to active processing within an area (Fries et al. 2001; Jensen and Colgin, 2007), or functional integration among distributed neural elements (Varela et al. 2001). The special relationship between gamma and theta oscillations likely stems from intertwined thalamocortical mechanisms (Llinás et al. 1999). This can be evidenced by observation that cortical stimulation at a theta frequency can induce the integration of spatially segregated gamma oscillatory brain regions (see Llinás et al. 2005), and that high theta-band thalamocortical coherence in patients expresses systematic relations to gamma rhythms recorded from cortex (Sarnthein and Jeanmonod, 2007). Considered in concert, such results also suggest that thalamocortical dialogue is essential for theta- and gamma-band cortical network dynamics supporting cognition and perception (Ribary, 2005). From such an outlook, it becomes apparent that theta oscillations may function to integrate gamma oscillatory cell coalitions into large-scale functional ensembles (von Stein and Sarnthein, 2000) through %:m phase locking (i.e. Tass et al. 1998). Locking of local gamma-oscillatory neuronal ensembles to theta rhythms may help to coordinate information transfer across longer distances as long conduction delays are less problematic for maintaining phase relations at low frequencies. This outlook is reinforced by findings that task dependent changes in theta oscillations encompass much broader cortical areas than do those involving gamma oscillations (Jerbi et al. 2009), suggesting that spatially expansive cortical theta rhythms may act as a "carrier wave" to integrate distant gamma-oscillatory ensembles. This likely explains our finding that gamma-band synchrony between a pair of activated regions is often modulated by theta phase in another region. In the present study, modulation of gamma-band synchronization between cortical regions by the phase of theta oscillations may reflect low frequency mechanisms for coordinating high frequency neural assemblies within a spatially distributed functional network underpinning auditory attention control.

Fig. 6 - An example of modulation of inter-regional gamma-band synchronization by theta phase. Depicted is modulation of 40 Hz PLV between superior temporal gyrus (STG) and superior parietal lobule (SPL) by the phase of theta oscillations in SPL in both hemispheres for both the shift-left and shift-right conditions. Red lines indicate inter-regional gamma-band phase locking at each point in the theta cycle. The dotted lines denote statistical confidence intervals (p<0.05) obtained from the surrogate distribution and black lines indicate the mean of the surrogate distribution.
The auditory system does not exhibit the same degree of lateralization as the visual system, which in the latter case enables clear delineation of lateralized patterns of inter-regional synchronization using EEG (Doesburg et al., 2008, 2009b). Nonetheless, it is likely that the lateralization differences we did observe are attributable to interhemispheric differences in the attention control system (Gainotti 1996), and to lateralization effects in the expression of theta rhythms during covert auditory attention orienting (Thorpe et al. 2011). We believe that our results illuminate specific attributes of cross-frequency mechanisms relevant to sculpting the flow of information within a transient network of functionally integrated cortical regions. It is not possible to discern from the results of the present study whether our source localization using theta-weighted beamformer analysis led to a greater propensity to identify regions involved in theta-gamma interactions. Further research will be required to address this question. Moreover, recent research has indicated that functionally-relevant coupling among oscillations in different frequency ranges is complex and involves interactions other than those between theta- and gamma-band oscillations (i.e. Miller et al. 2010; Voytek et al. 2010). Cross-frequency interactions in inter-regional phase locking other than theta/gamma have also been reported (Palva et al., 2005, 2010a, 2010b). Such findings indicate that future research will be required to fully delineate the interactions between local oscillations and inter-regional synchronization in distinct frequency ranges underlying information processing and network integration during cognition and perception. The observed spatial pattern of modulation of inter-regional gamma synchrony within the attention control network was complex. The emergence of complex cognitive acts from interactions among distributed neural populations is likely to involve sequential, and often reciprocal, exchanges of information. This suggests that the progression of inter-regional synchronization, and its organization through cortical theta rhythms, may show an ordered evolution throughout the network of activated brain regions. Future research focused on analysis of cortical network dynamics within specific stages of processing will be required to investigate this difficult problem.

4. Experimental procedures

To investigate inter-regional gamma-band synchronization during auditory attention control, we employed data previously published elsewhere by Green et al. 2011 and Störmer et al. 2009, for which localization of task-dependent activation of cortical regions underlying attention control was available based on previous analysis (see Green et al. 2011).

4.1. Subjects

Seventeen university students participated in the study. Data collected from three subjects were excluded from analysis due to excessive ocular artifacts. The remaining fourteen participants (mean age=20.1 years, SD=1.9; 8 females) all reported normal hearing and normal or corrected-to-normal vision. All participants provided written informed consent and the study was approved by the Simon Fraser University ethics committee.

4.2. Stimuli and experimental paradigm

Subjects performed the covert auditory attention orienting task (see Fig. 1) in an unlit electrically-shielded sound-attenuated chamber. Stimuli were presented using a 19-inch CRT computer monitor and two flanking loudspeakers. Subjects were seated 65 cm in front of the display and instructed to maintain visual fixation on a centrally located gray cross (0.9°×0.9°). Each trial began with a 100 ms auditory cue. Two-thirds of trials were target trials. On shift-cue trials (67% of target trials) subjects were directed to attend to the left or right side depending on the direction of the frequency sweep in the cue. For half of the subjects ascending frequency sweeps (750–1250 Hz) were used to cue attention to the left, and descending frequency sweeps (750–1250 Hz) were used to cue attention to the right. For the other half of the subjects this was reversed. On neutral-cue trials (33% of target trials), which consisted of simultaneous upward (750–1000 Hz) and downward (1250–1000 Hz) frequency sweeps, subjects were instructed to maintain attention at fixation and not shift attention. Cues were presented simultaneously from both speakers and were perceived to emanate from the location of the fixation cross. Following an 800 ms stimulus onset asynchrony (SOA) a target sound was presented to either the left or right side with equal probability. Target stimuli consisted of 100 ms duration white noise bursts with either a 5 ms or a 20 ms period of silence in the middle. Subjects were instructed to press the left button on a mouse if the target stimulus contained a short gap, and to press the right button when the target stimulus contained a long gap. All subjects responded using their right hand. Cues were noninformative regarding the location of the subsequent target sound but subjects were told to attend to the cued side to help them perform the discrimination task. Target presentation was followed by a 1400 ms inter-trial interval. All cue and target stimuli were presented at 70 dB SPL at subjects’ ear location. A secondary probe task was implemented on one third of all trials to assess whether subjects paid attention to the cued location. On these trials, a probe stimulus (cowbell, 350 ms duration, 72 dB SPL) was presented in lieu of a target. Subjects were instructed to respond to the probe only if it occurred on the cued side (thus no response if probe on uncued side or cue was neutral). Altogether, the experiment comprised 25 blocks each containing 36 trials.

4.3. EEG recording

EEG data were acquired using a modified 10–10 montage comprised of 63 tin electrodes referenced to the right mastoid (Green et al. 2008). Eye movements were detected using bipolar recordings positioned lateral to the right and left external canthi. Electrode FP1 was used to detect blinks. Electrode impedances were kept below 10 kΩ. Data were bandpass filtered 0.1–100 Hz and digitized at 500 Hz. Ocular and nonocular artifacts were identified using a semi-automated procedure (see Green et al. 2008), and data epochs containing artifacts were excluded from analysis. This resulted in 3482 left-cue trials, 3510 right-cue trials, and 3513 neutral trials for analysis. All subjects had a minimum of 70% of trials retained in each condition after artifact removal.
4.4. Beamformer source localization

Beamformer analysis was performed on each subject’s data using the Multiple Source Beamformer implemented in the Brain Electrical Source Analysis software (BESA 5.1; Megis Software, Germany), implementing a spatial filter and producing a three dimensional estimate of activity throughout the brain (Gross et al. 2001; Green and McDonald, 2009; Van Veen et al. 1997). Cortical activity underlying the control of auditory attention was localized by constructing source estimations for theta band (4–7 Hz) activity in each shift condition (left and right), normalized relative to theta activity in the neutral (no shift) cue condition. Theta weighted beamformer analysis was employed as previous work has demonstrated that this is a highly effective means for revealing distributed network activation during covert orienting using scalp EEG (Green and McDonald, 2008; Green et al., 2011). This procedure was implemented in order to reveal the location of cortical activations underlying the control of auditory attention, rather than that relating to processing of the physical characteristics of the auditory cue. The procedure was performed for 18 separate 50-ms time windows spanning the cue-target interval. Beamformer output from each time window was subjected to non-parametric statistical analysis using permutation tests to identify cortical activity that was significant across subjects (Singh et al. 2003). Importantly, beamformer analysis also attenuates oscillatory activity generated from artefactual sources such as eye movements. Results of the beamformer analysis were previously published in Green et al. 2011, and additional detail regarding these methods is available there.

4.5. Inter-regional synchronization

We extracted broadband time series using a dipole source montage in which locations were assigned to the activation peaks for statistically significant sources. The source waveforms were created using an algorithm that excludes contributions from other modeled sources and limits the contributions of noise and non-modeled source activity to source activity (BESA 5.1; Megis Software, Scherg et al. 2002). Epoched broadband time series extracted from each cortical generator were then filtered at from 6 to 60 Hz at 1 Hz intervals (passband $= \pm 0.05f$, where $f$ represents the filter frequency). The analytic signal

\[
\phi(t) = f(t) + i\tilde{f}(t) = A(t)e^{i\phi(t)}
\]

of the filtered waveform was then calculated for each epoch $f(t)$, where $f(t)$ is the Hilbert transform of $f(t)$ and $i = \sqrt{-1}$, to obtain the instantaneous phase, $\phi(t)$, and amplitude, $A(t)$, at each sample point. Time series of instantaneous amplitude values obtained in this manner were employed to index local activity at particular frequencies for activated sources.

Inter-regional synchronization of oscillations was measured using phase locking values (PLVs). PLVs were computed from the differences of instantaneous phases for pairs of time series from the reconstructed sources, for example, sources $j$ and $k$, at each time point, $t$, across $N$ epochs (Lachaux et al. 1999):

\[
PLV_{jk}(t) = N^{-1} \left| \sum_{n=1}^{N} e^{i(\phi_n(t)-\phi_k(t))} \right|
\]

As our goal was to separate oscillatory network dynamics underlying auditory attention control from those related to processing of the physical properties of the cue, as well as to maintain consistency with the analysis approach used in the beamformer source localization, we computed PLV differences between the shift-cue condition and the neutral-cue condition using methods described in Doesburg et al. 2009b. To this end, we calculated PLVs for each source pair in both to-be-compared cue conditions. PLVs are expressed as values between 0 (random phase difference) and 1 (constant phase difference) and were calculated for each time point in the analyzed epochs. We then subtracted PLVs from the neutral-cue condition from those in the shift-cue conditions (shift-left or shift-right) for each time point, producing a set of time series of difference PLVs (DPLVs) for each pair at each analyzed frequency. DPLVs were then standardized relative to a 250 ms pre-cue baseline

\[
DPLV_{jk}(t) = \frac{DPLV_{jk}(t)-DPLV_{jk,mean}}{DPLV_{jk,Bsd}}
\]

where $DPLV_{jk}(t)$ represents normalized DPLV at a given time point and $DPLV_{jk,mean}$ and $DPLV_{jk,Bsd}$ are the mean and standard deviation of the baseline period, respectively. The resulting measure, $DPLV_{jk}(t)$, indexes increases and decreases in inter-regional synchronization associated with attention control. Inter-regional synchronization was assessed only for source pairs that are anatomically connected (STG-IFG synchronization was not assessed).

To assess the statistical reliability of differences in inter-regional synchronization between the shift and neutral conditions we employed a multi-stage analysis procedure. We first employed the surrogate statistical method (Lachaux et al. 1999) to assess the DPLVs. This procedure involved shuffling the data epochs for a particular source pair between the two conditions and computing DPLVs for the resulting dataset. This process was repeated 200 times to create a surrogate distribution against which the experimental DPLVs could be compared. The percentile rankings of the data-derived DPLVs within the surrogate distribution were then used to identify significant increases in synchronization. As performing a large number of statistical tests in a single experiment increases the risk of Type I errors, we imposed a number of additional criteria for determining significant increases in gamma synchronization in an effort to reduce false-positive results. To this end, we divided the cue-target interval into 50 ms time bins, identical to those used in the beamformer analysis (see Green et al. 2011), and determined which bins contained significant increases in synchronization relevant to the orienting of auditory spatial attention. For a time bin to be considered significant, both of the following criteria had to be met: (i) a minimum of 12 ms (three consecutive time points) of consecutive increased synchronization (see Murray et al. 2004 for a similar approach with ERP data) above 1.5 SD in the average DPLV; (ii) a minimum of 12 ms of consecutive synchronization above the 97.5th percentile cutoff in the surrogate distribution ($p < .025$) in each hemisphere.

4.6. Theta modulation of inter-regional gamma-band phase locking

To assess the modulation of inter-regional gamma-band synchronization by theta phase we sorted gamma-band PLVs
between two regions identified in the beamformer analysis by the phase of theta oscillations in one localized source, using methods established in Doesburg et al. 2009a. This analysis included each time point in the cue-target interval and all analyzed epochs. We sorted gamma (40 Hz) inter-regional phase-locking between two cortical sources by theta phase (6 Hz) in one source. We employed 6 Hz and 40 Hz signals with a passband of passband=§±0.05f in order to maintain methodological consistency with our calculation of inter-regional synchronization, and to employ established techniques which have previously revealed modulation of interregional gamma synchrony by theta phase (Doesburg et al. 2009a). Gamma PLVs were sorted into 60 bins (0.105 radians width) and mean gamma PLV was calculated for each bin. Statistical significance was assessed using the surrogate statistical method. Surrogate distributions were constructed by randomly shuffling theta time series and computing mean gamma PLVs in each bin. This process was repeated 1000 times and modulation of gamma PLV by theta phase was considered statistically significant (p<0.05) if mean gamma PLV was above the 97.5th percentile, or below the 2.5th percentile of amplitude values in the surrogate distribution for at least two adjacent bins. Between-condition difference values were not employed in our analysis of cross-frequency interaction as subtracting phase across experimental conditions would not be a meaningful comparison. For similar reasons data were also not standardized relative to the pre-cue baseline period for this analysis.

**Acknowledgments**

This research was supported by grants from the Natural Sciences and Engineering Research Council (NSERC) of Canada to J.J.M. and L.M.W., an NSERC Graduate Scholarship to J.J.G., and a Michael Smith Foundation Postgraduate Fellowship to S.M.D. We thank Keiichi Kitajo for providing original MATLAB code that we revised to accomplish the cross-frequency analysis.

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