**Title:** Macroscopic cortical and head anatomy predicts inter-individual differences in visually induced gamma amplitude but not peak frequency

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**Abstract:** The visually induced gamma band (40-90Hz) response varies within a healthy population in both amplitude and peak frequency. Due to the wide range of literature linking gamma amplitude and peak frequency to behavior, cognition/perception, and mental illness, in recent years several studies have sought to establish the basis of gamma amplitude and peak frequency in the healthy brain using structural and functional MRI, achieving mixed results. To further address this, we compared gamma amplitude and peak frequency in two groups of healthy humans (n=24, n=9) with MRI-derived structural measures such as distance from electrode to active cortex, dipole cancellation over active cortex, curvature of active cortex, and functional measures such as extent of BOLD activation, and BOLD percent change. We find that of these measures, gamma amplitude best correlates with distance from electrode to active cortex and intrinsic curvature of active cortex, while under specific stimulus conditions, gamma peak frequency correlates with extent of BOLD activation. We propose that inter-individual differences in gamma amplitude are driven by differences in macroscopic cortical anatomy, while differences in peak frequency are unaffected by anatomy and more closely related to functional differences across individuals.

**Introduction:**

Electroencephalography (EEG) measures fluctuations in electrical potential on the surface of the scalp (Nunez and Srinivasan, 2006), which often occur in narrowly defined frequency ranges, leading to the classification of these fluctuations as brain rhythms (Buzsáki et al., 2012). Despite the nearly 100 year history of EEG (Berger, 1969), much remains to be understood about the biophysical and anatomical basis for brain rhythms observed from the surface of the scalp (Cohen, 2017). In EEG literature, it is typically assumed that these rhythms arise from synaptic currents along the soma and dendrites of pyramidal cell neurons, resulting in the formation of electrical dipoles in an open field arrangement which, when the neural activity is synchronous, allows a signal to be detected on the scalp (Ahlfors et al., 2010; Irimia et al., 2012; Murakami and Okada, 2006; Musall et al., 2014). This dipole model explains the scalp potential as a function of four variables 1) distance from dipole to measurement location 2) orientation of dipole 3) current strength of dipole and 4) conductivity of extracellular medium surrounding the dipole. While the dipole model serves as the basis for a large body of literature attempting to relate scalp potentials to cortical activity (Gramfort et al., 2010), to date no study has empirically examined the degree to which variables such as distance and cortical curvature affect inter-individual differences in brain rhythms.

One of the most reliably elicited and commonly studied brain rhythms is the high frequency (40-90Hz, ref) rhythm otherwise known as the gamma band rhythm (Hoogenboom et al., 2006). In particular, the visually induced gamma band response has recently been shown to co-vary strongly with a number of perceptual phenomena (Gray et al., 1990), neurological disorders (refs), and is also thought to underlie changes in the blood oxygen level dependent functional magnetic resonance imaging (BOLD FMRI) signal (Logothetis et al., 2001) although see (Butler et al., 2017a; Swettenham et al., 2013) for opposing evidence. As such, understanding the anatomical basis for inter-individual differences in healthy human visually induced gamma band response is of considerable interest.

The visually induced gamma band response is commonly described using two metrics 1) amplitude and 2) peak frequency. Amplitude represents the strength of the signal in a given frequency range, and is typically defined as the difference in signal strength from task to rest at each frequency. Peak frequency is defined simply as the frequency at which amplitude is highest. Amplitude and peak frequency are thought to provide different indices of neural activity due to the fact that they are dissociable in both experimental (Jia et al., 2013) and modeling (ref) work, although a complete understanding of the neuronal generators giving rise to gamma power and peak frequency is still lacking (ref).

While much remains to be understood about how gamma amplitude and peak frequency arise from neuronal circuits, empirically these metrics are known to co-vary with a number of cognitive disorders, such as schizophrenia and autism. For example, schizophrenia has been shown to result in reduced gamma amplitude over a number of experimental paradigms (Tan et al., 2013). Interestingly, while gamma amplitude is also reduced in autism (Simon and Wallace, 2016) there is evidence for increased peak frequency with increasing levels of autistic traits (Dickinson et al., 2015) which may provide a neurophysiological correlate for some of the enhanced visuospatial abilities observed in autism (Dickinson et al., 2016; Mottron et al., 2006). In any case, evidence from twin studies points toward a strong genetic basis for inter-individual differences in the gamma rhythm (van Pelt et al., 2012), which could indicate an anatomical origin for the gamma rhythm deficiencies observed in autism and schizophrenia. This is further supported by the fact that gamma rhythms are stable within individuals across both hours and days (Muthukumaraswamy et al., 2010) suggesting that differences in gamma across subjects are not due to behavioral variables such as attention, as some claim (Womelsdorf and Fries, 2007).

A number of studies have directly investigated the anatomical basis for healthy human variability in visually induced gamma amplitude and peak frequency. The original investigation into peak frequency reported a positive correlation between magnetic resonance spectroscopy (MRS) GABA concentration in occipital cortex and gamma peak frequency (Muthukumaraswamy et al., 2009). The authors suggested that increased GABA concentrations reflect increased inhibition in V1, driving the peak frequency higher according to some modeling work (Brunel and Wang, 2003). However, a replication attempt using similar but not identical methodology with a much larger group of subjects found no such relationship (Cousijn et al., 2014) and subsequent work suggests that increased GABAergic activity actually leads to decreased peak frequency (Magazzini et al., 2016). More recently, the original positive MRS GABA vs peak frequency correlation was replicated (Kujala et al., 2015) but using completely different methodology (GABA receptor density using positron emission tomography (PET)) and small sample size (n=10).

Another correlate of visually induced gamma peak frequency which has been proposed is the surface area of retinotopically defined primary visual cortex (V1), which has been shown to also correlate positively with gamma peak frequency (Schwarzkopf et al., 2012). This was explained using the theory of coupled oscillators (Breakspear et al., 2010), where the higher peak frequency in subjects with larger V1 surface area was thought to be due to greater local homogeneity in cortical columnar architecture. While this finding relating surface area to peak frequency was not replicated on a different group of subjects (Robson et al., 2015), the latter study did not base their measure of surface area on functionally defined regions of interest. A replication attempt by the same authors as the original paper (Gregory et al., 2016) yielded the same positive correlation, suggesting that methodology may be an important factor.

With respect to gamma amplitude, to our knowledge only one study has shown a significant anatomical correlate (Kujala et al., 2015) where a negative correlation between inter-individual GABA receptor density and gamma band amplitude was reported. All other studies found no relationship between any of the anatomical measures and gamma amplitude including cortical surface area (Schwarzkopf et al., 2012), GABA concentration (Cousijn et al., 2014), occipital volume, or thickness (Muthukumaraswamy et al., 2010). It should be noted that in (Gaetz et al., 2012) a significant positive correlation between gamma amplitude and the evoked response was found, which the authors attributed to signal to noise differences in subjects due to distance from cortex to MEG sensors.

In summary, with respect to the anatomical correlates of gamma amplitude and peak frequency, there is a lack of consensus in the literature regarding peak frequency, and as only one study has reported a significant relationship between gamma amplitude and anatomy, a lack of information regarding gamma amplitude. We therefore set out to investigate the anatomical correlates of both gamma amplitude and peak frequency using measures derived from a combination of structural and functional MRI. As mentioned earlier, the neuronal origin of the scalp potential is modeled as an electric dipole oriented perpendicular to the cortical surface, and hence depends on distance, orientation, current, and conductivity. We were unable to address inter-individual differences in dipole current or extracellular conductivity using our methods. Instead, we examined the effects of orientation using several curvature metrics (both intrinsic and extrinsic curvature) (Van Essen and Drury, 1997), and cortical cancellation (Irimia et al., 2012), and the effects of distance using distance from cortex to electrode (Butler et al., 2017b). We also examined how the extent and %change of a BOLD activation was correlated to inter-individual differences in gamma amplitude and peak frequency.

We hypothesized that gamma amplitude would be inversely correlated to distance and curvature, due to the physics underlying the scalp potential equation, while, based solely on previous reports (Gregory et al., 2016; Schwarzkopf et al., 2012), gamma peak frequency would be positively correlated to extent of BOLD activation.

**Methods:**

**Subjects:** The data was acquired as part of a larger study at the institute involving two separate acquisition protocols. The MRI/FMRI and EEG subjects from the large group (n=24) were acquired during separate EEG and FMRI scanning sessions, while the subjects from the small group (n=9) were acquired during a simultaneous EEG-FMRI recording session. Of the 24 subjects participating in the large group study, 3 were also present in the small group study, for a total of 30 unique subjects (13 female, no psychiatric or neurologic symptoms at the time of scanning or in the past, normal or corrected to normal vision). Informed consent was obtained according to the guidelines of the Internal Review Board of the Centre Hospitalier Universitaire de Sherbrooke.

**Stimulus construction and presentation:** All stimuli were generated using Psychophysics Toolbox (BRAINARD, 1997) and presented on a gray background with luminance equal to the mean luminance of the stimulus. For the large group, all stimuli were variations of a drifting sinusoidal grating, which had the following parameters: spatial frequency 3cycles/degree, temporal frequency 6 cycles/second, drifting from right to left within a 7 degree circular aperture in the center of the subject’s visual field. Six separate stimuli (Figure 1A) were used to induce a wide range of gamma responses 1) unperturbed (described above), 2) 5% contrast, 3) 33% contrast, 4) plaid, 5) 10% randomized, 6) 60% randomized. Details on stimulus construction are available in a previous publication (Butler et al., 2017a). For the small group, three separate stimuli were used 1) unperturbed, 2) 10% randomized 3) 100% randomized, and stimulus construction was identical to the that of the large group, with the exception that stimuli were presented using a full field aperture rather than a 7 degree circular aperture. Within the scanner, stimuli were projected from an MRI-compatible monitor (800x600 pixels, frame rate 75Hz) to a mirror positioned above the subject’s face attached to the head coil. For the large group, 45 trials/stimulus type were presented (270 trials per subject), with a 2 second presentation duration, and 14 second inter-stimulus interval (ISI). For the small group, 32 trials/stimulus type were presented (96 trials per subject), with a 5-second stimulus duration and ISI of 3-5 seconds (randomly jittered). Outside the scanner, EEG was recorded for the large group only, stimuli were presented on a CRT monitor (800x600 pixels, frame rate = 85Hz), at a rate of 1 stimulus every 5 seconds, (2 second presentation duration, 3 second ISI), each of the 6 stimulus types was presented 135 times (810 trials per subject).

**MRI acquisition and preprocessing:**

**Acquisition:** Whole brain FMRI volumes were acquired on a 3T MRI scanner (Ingenia, Philips Healthcare) using a 32 channel head coil for reception. The FMRI sequence parameters differed slightly from large group to small group. Large group (n=24) sequence parameters: TR/TE = 2000/30ms, flip angle=70deg, FOV=224x224x136.5mm, voxel size = 3.5mm isotropic, no multiband. Small group (n=9) sequence parameters: TR/TE = 693/30, flip angle=50deg, FOV=240X240X123.75mm, voxel size=3.75mm isotropic, multiband factor 3. An anatomical T1-weighted 3D gradient-echo image (TR/TE=7.9/3.5ms, flip angle = 8deg, FOV=240x240x150mm, voxel size = 1mm isotropic) was acquired following FMRI acquisition sessions for both groups.

**EEG recording and preprocessing:**

**Large group (n=24) recording:** Scalp signals were acquired on a 64 channel EEG actiCap system (Brain Products) at 500Hz referenced from electrode Fz according to the 10-20 system. The cap was positioned by the experimenter according to the following anatomical landmarks: electrode Oz directly superior to the inion, and the midpoint between electrodes Cz and reference on the apex of the head. **Preprocessing:** Poorly connected electrodes were isolated using visual inspection of the raw electrode time series, and interpolated using spherical interpolation (ref, EEGLAB). To maximize the signal to noise ratio (SNR) of the EEG gamma band response, temporal independent component analysis (ICA) (Delorme and Makeig, 2004) was performed on each subject separately after applying a 1-120Hz bandpass filter and epoching from -1:3 seconds relative to stimulus onset of each trial. ICA components were then visually inspected for each subject, and a small subset (2-5 components per subject) were selected based on the presence of a narrow band gamma response and/or weight maps with dipolar-like topography constrained to the posterior electrodes (figure sup.). Signal from these gamma band components was projected back to channel level using the inverse weight matrix, to yield artifact free channel level EEG signals in each subject.

**Small group (n=9) recording:** Scalp signals were acquired on a 63 channel MR-compatible EEG cap (Brain Products) sampling at 5000Hz referenced from electrode Fz according to the 10-20 system. Impedances were reduced to values below 20kOhm at each electrode prior to placing the subject in the MR scanner, and monitored throughout the recording. The cap was positioned according to the same anatomical landmarks as in the large group, by the same experimenter, and electrodes were precisely localized using an ultra-short echo time sequence (Butler et al., 2017b) which is capable of directly imaging the plastic materials of the EEG cap. **Preprocessing:** MRI artifacts (FMRI gradient artifact and ballistocardiogram artifacts) were removed using the sliding window average artifact subtraction approach (Allen et al., 2000) as implemented in BrainVision Analyzer software. ICA denoising was then performed on MRI-artifact cleaned data in an identical fashion as for the large group.

**Analysis:**

**Gamma amplitude:** After ICA denoising and back projection to channel level, EEG gamma amplitude was defined at each channel separately for each subject and stimulus type: the Fast Fourier Transform (FFT) was computed for both baseline (-1000ms to 0ms) and task (0ms to 2000ms for large group, 0ms to 5000ms for small group). Baseline FFT amplitude was then subtracted from task FFT amplitude at each frequency band separately, yielding a spectrum of Fourier coefficient differences from task to rest. Gamma amplitude was then defined at each electrode as the mean difference between task and rest from 40-90Hz. A single gamma amplitude value was obtained in each subject by averaging amplitude over all posterior electrodes (P, PO, and O) and stimulus types.

**Gamma peak frequency:** Gamma peak frequency was defined at the ICA component level rather than the channel level. In order to isolate a single, robust gamma peak frequency in each subject only the unperturbed and 10% randomized grating stimuli were used, as both induced a single, strong gamma peak in the 40-90Hz range for all subjects who were gamma responders (defined below). This was in contrast to the plaid or 60% randomized stimuli, which resulted in a double peak or a strong blurring of the gamma peak respectively, and not suitable for gamma peak frequency estimation. Event-related spectral perturbation (ERSP) was computed on ICA component time series in partially overlapping 250ms Hanning windows (Delorme and Makeig, 2004) at 200 separate time points yielding ERSP for each ICA gamma component. For each subject, the ERSP was then averaged across ICA components (2-5 per subject), stimulus types (unperturbed and 10% randomized) and stimulus duration (500-2000ms large group, 500-5000ms small group). The initial 500ms was not included in peak frequency estimation, to avoid stimulus onset effects and include only the peak during the sustained narrow-band gamma response. The gamma peak frequency for each subject was then defined as the frequency band between 40-90Hz with the highest amplitude. **Removal of “non-responders” when computing gamma peak frequency:** Although subjects with a complete absence of gamma power in response to the stimulus are of interest when investigating gamma amplitude, it is impossible to define a peak frequency subjects with no discernible gamma peak. A “gamma responder” was hence defined as a subject with a stimulus induced db increase greater than 0.5 at any frequency in the gamma range.

**FMRI regions of interest:** An FMRI region of interest (ROI) was defined in each subject separately by convolving a stimulus design time series with a hemodynamic response function (HRF) (Friston et al., 1994) and correlating the HRF-convolved time series with the FMRI signal in each voxel. The whole brain correlation map was then thresholded to yield binary ROIs in each subject. In the large group, this threshold was r>0.5, and in the small group, r>0.25. The threshold was lower in the small than the large group due to the slightly different stimulus presentation paradigm (a shorter rest period, and a pseudo-random ISI between stimulus presentations in the small group), which resulted in overall weaker correlations for the small group. FMRI ROIs were then aligned to each subject’s anatomical T1 (1mm isotropic) (ref, epireg), where all subsequent analysis was performed.

**Distance from active cortex to electrode:** distance was defined at each electrode as the Euclidean distance from the center of mass of each subject’s FMRI ROI to the electrode location. To obtain a single distance measure in each subject, distance values across all posterior electrodes (P, PO, and O) were averaged, giving the mean distance from posterior electrodes to the center of functional activation. In the small group, distances were precise to within 1mm (Butler et al., 2017b) as the electrode locations were measured directly using the UTE MRI sequence. In the large group, locations were obtained by the following procedure: UTE localized coordinates from each subject in the small group were mapped to the MNI152 anatomical template (Evans et al., 2012) based on a 12 DOF affine transform from each subject’s T1 (Jenkinson et al., 2012). Small group coordinates were then averaged across all subjects, to create an electrode coordinate template in the MNI152. The electrode coordinate template was then mapped to each subject in the large group, again using a 12 DOF affine transform based on the T1.

**Metrics of cortical morphometry (intrinsic curvature, mean curvature, cancellation index):** Intrinsic curvature and mean curvature were obtained using Freesurfer (Fischl, 2012). As Freesurfer defines these values based on cortical parcellations, we isolated the Freesurfer defined cortical parcel with the largest overlap with our FMRI ROI, which happened to be the lateral occipital cortex (surprisingly, 60% of lateral occipital voxels were contained within the FMRI ROI, while only 35% of calcarine sulcus voxels). Intrinsic curvature (curvInd) and mean curvature (meancurv) of lateral occipital cortex were then extracted from freesurfer output using text file processing, and averaged across hemispheres in each subject. The cancellation index (I0) was defined as in (Irimia et al., 2012), higher values of I0 indicate that . The normal vectors used to calculate I0 were obtained by intersecting the Freesurfer white matter surface normals with each subject’s FMRI ROI mask. As I0 increases systematically with the number of normal vectors used in the calculation (Irimia), we arbitrarily restricted the number of normals in each subject to the 2000 normals in the region of strongest functional activation (ie, the 2000 normals in voxels with the highest correlation to the stimulus).

**Extent of BOLD activation and percent change:** The extent of BOLD activation was defined simply as the number of voxels remaining after applying a correlation threshold to the FMRI correlation map (see above). Percent change (%change) was defined as peak BOLD signal following stimulus onset minus the baseline BOLD signal, divided by the baseline ((task-rest)/rest, averaged across all stimulus types.

**Results:**

*Visually induced narrow band gamma was observed in 80% of healthy humans.* Single subject gamma responses are shown (Figure 1A, Figure 1B). For visualization purposes, each subject’s response to unperturbed and 10%random stimuli were pooled and the average displayed in these plots. Based on the criteria defined in (Methods, gamma peak frequency), 24/30 or 80% of subjects can be defined as “gamma responders”.

*Inter-subject gamma amplitude is consistent across stimulus types.* To justify pooling of gamma amplitude in response to different stimulus types before correlating with anatomy, we examined the inter-subject correlation of gamma amplitude across stimulus types. We find that, despite the wide range of gamma amplitude response across stimulus types (Figure 1C), there was strong correlation of inter-subject gamma amplitude across stimulus types (Figure 1D, p<0.0001). That is to say, subjects with a high amplitude gamma response to one stimulus type were also high amplitude responders to all other stimuli.

*Inter-subject gamma amplitude and distance from cortex to electrode are inversely correlated.* There was a significant inverse relationship between distance from electrode to active cortex and gamma amplitude in the large group (Figure 2A, rho=-0.48, p=0.016) and a strong trend for the small group (Figure 2A, rho=-0.59, p=0.091).

*Gamma amplitude is inversely related to all curvature metrics, but no significant relationship between amplitude and mean curvature or cortical cancellation.* There was a significant inverse relationship between intrinsic curvature and gamma amplitude in the large group (Figure 2B, rho=-0.49, p=0.015), and a similar trend that did not reach significance in the small group (Figure 2B, rho=-0.26, p=0.493). There was no significant relationship between the cortical cancellation index (I0) and gamma amplitude in either large (Figure 2C, rho=-0.18, p=0.387) or small (Figure 2C, rho=-0.14, p=0.711) groups. Similarly, there was no significant relationship between extrinsic (mean) curvature and gamma amplitude in either large (Figure 2D, rho=-0.22, p=0.304) or small (Figure 2D, rho=-0.38, p=0.311) groups.

*Intrinsic curvature and distance are positively correlated to each other and overall gray matter volume.* There was a significant positive correlation between intrinsic curvature and distance from cortex to electrode for large group (r=0.47, p=0.02) and a clear trend in the small group (r=0.6, p=0.088). Both intrinsic curvature and distance were also positively correlated to total gray matter volume in large group (distance vs gray matter volume rho=0.51, p=0.009, intrinsic curvature vs gray matter volume rho=0.52, p=0.008) and small group (distance vs gray matter volume rho=0.89, p=0.001, intrinsic curvature vs gray matter volume rho=0.55, p=0.11). Despite this, overall gray matter volume was not correlated with gamma amplitude in large (rho=-0.22, p=0.298) or small (rho=-0.29, p=0.43) groups.

*Gamma peak frequency is positively correlated to extent of BOLD activation under specific stimulus conditions.* When removing “non-responders” from the large group (where the stimulus was masked by a 7deg circular aperture), there was a highly significant correlation between peak frequency and the extent of BOLD activation (Figure 2D, rho=0.70, p=0.001), however this was not present in the smaller group (where a full field stimulus was presented) (Figure 2D, rho=-0.02, p=0.955). When including all subjects in the large group, the correlation was weaker but still significant (r=0.47, p=0.022). There was no correlation between peak frequency and any of the structural measures (distance (large group p=0.86, small group p=0.98), intrinsic curvature (large group p=0.47, small group p=0.37), mean curvature (large group p=0.74, small group p=0.70), or cancellation (large group p=0.39, small group p=0.79)).

*Neither BOLD %change or extent of BOLD activation are correlated to gamma amplitude.* There was no correlation between %change and gamma amplitude for large group (rho=0.26, p=0.21) or small group (rho=0.14, p=0.71). Similarly, there was no correlation between gamma amplitude and extent of BOLD activation (large group p=0.87, small group p=0.78). There was a trend towards a positive correlation between %change and peak frequency in the large group (rho=0.34, p=0.09) but not in the small group (rho=-0.2, p=0.59). Tables of rho/p between gamma amplitude/peak frequency and all structural metrics are also presented (Figure 2F, Figure 2G).

**Discussion:**

The anatomical basis for inter-individual differences in the healthy human visually induced gamma band response has been investigated. In contrast to previous studies (Cousijn et al., 2014; Gaetz et al., 2012; Kujala et al., 2015; Muthukumaraswamy et al., 2009; Robson et al., 2015; Schwarzkopf et al., 2012), we focused mainly on anatomical variables likely to affect gamma amplitude rather than gamma peak frequency, although peak frequency was investigated as well. The gamma rhythm is a complex neurophysiological phenomenon that is still not fully understood (modeling refs), but we hypothesized that inter-individual differences in non-invasively measured healthy human gamma amplitude may be explained in large part by differences in macroscopic brain anatomy.

Our first two results provide further indirect evidence that gamma amplitude is related to macroscopic structural metrics. First, we note that roughly 20% of subjects can be classified as “non-responders”, this is also roughly in accordance with other reports on the ratio of “non-responders” in the visually induced gamma band response (Muthukumaraswamy et al., 2010; Scheeringa et al., 2016). All our subjects were healthy humans with normal or corrected to normal vision, so the lack of a gamma response in 20% of subjects points strongly to differences in anatomy as the underlying cause. Furthermore, in all “non-responders” a clear alpha/beta desynchronization was observed, indicating that the lack of gamma response was not due to attentional deficits. Second, inter-individual gamma amplitude was highly correlated across stimulus types, which is to say, subjects who respond strongly to the plaid, also responded strongly to unperturbed, or 10% randomized, etc. This suggests that the same underlying anatomical factors are affecting each individual’s gamma response across a range of stimuli.

The most robust correlation noted here is the inverse relationship between gamma amplitude and mean distance from center of BOLD activation to electrode. This result was noted in both subject groups, and makes sense from a purely physical standpoint, as the electric field arising from a dipole is known to fall off as 1/r^2 (Nunez and Srinivasan, 2006). Clearly, inter-individual variation in gamma rhythm amplitude is no exception to this fundamental law of nature. Unfortunately, due to limited imaging processing methods we were unable to investigate the effects of different tissue layers on distance (ie, is the distance correlation driven by thicker skull, meninges, or scalp), but this provides an interesting question for future research. While this is the first study empirically demonstrating a relationship between distance and gamma band amplitude, it was hinted at in earlier work (Robson et al., 2015) where a positive association was found between inter-subject event-related field and gamma amplitude, and this co-variance was attributed to distance from MEG sensor to cortex.

We also investigated the relationship between different indices of cortical curvature and gamma amplitude. Only one of these indices (Intrinsic curvature) correlated significantly with gamma amplitude. However, it is worthwhile to note that all correlations between curvature and amplitude were negative, and the null result for mean curvature and cortical cancellation could be due to the small sample sizes used here (n=24 and n=9). Interestingly, we find that the cortical cancellation index has the weakest relationship to gamma amplitude of all curvature metrics, instead, it appears as if more local curvature metrics (Van Essen and Drury, 1997) have a larger effect on the gamma rhythm. Cortical folding abnormalities have been reported in disorders such as autism (Nordahl et al., 2007), and the inverse relationship reported here between curvature and gamma amplitude may help to explain reduced gamma amplitude in autistic populations (Wilson et al., 2007).

We noted a robust correlation between intrinsic curvature and distance, and also that distance and intrinsic curvature were both correlated to total gray matter volume. These correlations can be explained by the fact that larger intrinsic curvature can be expected in larger brains (RONAN et al., 2011), and from a purely anatomical standpoint, subjects with larger brains are also likely to have larger heads (Bartholomeusz et al., 2002), which would increase the distance between electrode and cortex. Therefore, it is unsurprising that intrinsic curvature and distance are correlated across subjects. However, the correlation between intrinsic curvature and distance complicates the interpretation of the effects of these two metrics on gamma amplitude. It could be that the correlation between intrinsic curvature and gamma amplitude is driven by a “large brain effect” where subjects with larger brains have higher intrinsic curvature but also larger distances between scalp and cortex, and intrinsic curvature itself does not affect gamma amplitude.

Gamma peak frequency was also investigated. Peak frequency was unrelated to any of the structural parameters (distance, curvature) in either group, but in the large group we noted a strong positive correlation between peak frequency and extent of BOLD activation, and a trend towards positive correlation between peak frequency and %change. This result is interesting for two reasons. First, it shows that peak frequency is independent of macroscopic anatomical features which affect signal to noise across subjects, and can hence serve as a useful biomarker of functional processing in studies of neurodegeneration, cognitive disorders (ref, autism), or perceptual processing and second, helps to reconcile previously reported results and conflicting hypotheses on peak frequency.

To date, there are two main hypotheses addressing the basis of gamma peak frequency across a healthy population 1) peak frequency is driven by differences in GABA concentration (Kujala et al., 2015; Muthukumaraswamy et al., 2009), but see (Cousijn et al., 2014) and 2) peak frequency is driven by differences in surface area of visual cortex (Gregory et al., 2016; Schwarzkopf et al., 2012), but see (Robson et al., 2015). We believe that our result (extent of BOLD activation predicts gamma peak frequency) can reconcile both the positive and null results listed above. First, consider the studies reporting a positive relationship between gamma peak frequency and GABA concentration/receptor density. The study by (Muthukumaraswamy et al., 2009) employed a 3x3x3cm MRS voxel, and the PET study used an 18x18x21mm smoothing kernel on the data. Due the fact that V1 has a much higher concentration of GABA receptors than surrounding areas (Kujala et al., 2015), both of these methods (large voxel and smoothing) will result in strong partial volume effects (PVE) over the region of interest, and likely be influenced by the size of V1. In contrast, the MRS study reporting a null result (Cousijn et al., 2014) used a much smaller voxel (2x2x2cm, which is 1/3 the volume of a 3x3x3 voxel), and hence, less susceptible to PVE. Second, consider the two studies reporting positive associations between gamma peak frequency and V1 surface area (Gregory et al., 2016; Schwarzkopf et al., 2012); both studies used FMRI to retinotopically delineate primary visual cortex. In contrast, the study reporting a null result between peak frequency and surface area (Robson et al., 2015) relied on probabilistic anatomical boundaries, and did not delineate V1 using functional mapping. Taken together, these results all indicate that it is the size of functionally defined visual cortex that determines gamma peak frequency. We therefore take our results as tentative support for the surface area hypothesis, but providing strong evidence in favor of PVE being the underlying factor driving the GABA concentration correlations.

**Conclusion:** Subjects with flatter cortices that are closer to the surface of the scalp will tend to exhibit higher amplitude visually induced gamma band responses. Subjects with more widespread BOLD activation will exhibit higher gamma peak frequency, possibly due to the fact that more widespread BOLD activation reflects larger cortical surface area.

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