Functional and structural correlates of the aging brain: Relating visual cortex (V1) gamma band responses to age-related structural change

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Abstract

The gamma band response is thought to be a key neural signature of information processing in the mammalian brain, yet little is known about how age-related maturation influences the gamma-band response. Recent MRI based studies have shown that brain maturation is accompanied by clear structural changes in both grey and white matter, yet the correspondence of these changes to brain function is unclear. The objective of this study was to relate visual cortex (V1) gamma-band responses to age-related structural change.

We evaluated MEG measured gamma-band responses to contrast gratings stimuli and structural MRIs from participants observed from 2 separate research centers (MEG lab at CUBRIC, Cardiff University, UK, and the Lurie Family Foundations MEG Imaging Center, (CHOP) at the Children’s Hospital of Philadelphia). Pooled participant data (N=59) ranged in age from 8.7 to 45.3 yrs.

We assessed linear associations between age and MEG gamma-band frequency and amplitude, as well as between age and MRI volumetric parameters of the occipital lobe. Our MEG findings revealed a significant negative correlation for gamma band frequency vs. age. Volumetric brain analysis from the occipital lobe also revealed significant negative correlations between age and the cortical thickness of pericalcarine and cuneus areas.

Our functional MEG and structural MRI findings shows regionally specific changes due to maturation and may thus be informative for understanding physiological processes of neural development, maturation, and age-related decline. In addition, this study represents (to our knowledge), the first published demonstration of multi-centre data sharing across MEG centers.

Introduction

A growing body of research suggests that the gamma-band (~40 Hz) response is a key neural signature of information processing in the mammalian brain. Invasive and non-invasive imaging studies have shown primary cortical gamma-band reactivity to auditory (Gurtubay et al., 2004; Steinschneider et al., 2008), visual (Adjamian et al., 2004; Hoogenboom et al., 2006; Muthukumaraswamy et al., 2009; Muthukumaraswamy and Singh 2008), somatosensory (Bauer et al., 2006; Gaetz and Cheyne 2003), and motor tasks (Cheyne et al., 2008; Gaetz et al., 2010). Gamma-band responses have also been associated with higher-order cognitive functions such as attention (Fell et al., 2003; Muller et al.,...
2000), perception (Keil et al., 1999; Tallon-Baudry et al., 1997; Tallon-Baudry et al., 1996),
learning (Gruber, et al., 2001; Miltner et al., 1999) memory (Lutzenberger et al., 2002;
Tallon-Baudry et al., 1998) and are disturbed in psychiatric disorders such as schizophrenia
and autism (Lewis et al., 2005; Spencer et al., 2003; Uhlhaas and Mishara 2007). Gamma
oscillations have also been proposed as a fundamental mechanism for cortical computation
and long-range communication between brain areas (Fries 2009; Gregoriou, et al., 2009).

Despite the importance of gamma-band cortical oscillations, identifying an effective
stimulus to elicit a strong, artifact-free and reliable gamma-band response has been
challenging (Fries, et al. 2008). Recently, however, simple high-contrast visual stimuli have
gained prominence as a robust method to elicit cortical gamma-band activity in primate
electrocorticographic (ECoG) studies (Vinck, et al., 2010) and non-invasively using MEG
(Adjamian et al., 2004; Hoogenboom, et al., 2006; Muthukumaraswamy et al., 2009;
Muthukumaraswamy et al., 2010) in humans. In human MEG studies, vertical or concentric
circle high-contrast square-wave grating stimuli (~3 cycles per degree) are presented to
central vision, or a single hemifield. These stimuli induce a robust gamma-band response
from primary visual cortex (V1) that persists for the duration of the presented visual
stimulus. These gamma-band responses show high between-subject variability in amplitude
and frequency, however, within-subject repeated measures appear remarkably consistent
(Hoogenboom et al., 2006; Muthukumaraswamy et al., 2010). Similar between-subject
variability has been noted in ECoG (Rols et al., 2001) and LFP recordings (Lima et al.,
2010). Muthukumaraswamy et al. (2009) recently demonstrated that gamma-band frequency
was correlated with magnetic resonance spectroscopic (MRS) measures of gamma-amino-
butyric acid (GABA) concentration. In a study exploring repeatability of gamma cortical
oscillations, the same authors observed that gamma-band frequency tended to decrease with
age in a healthy adult population (Muthukumaraswamy et al., 2010).

MRI imaging studies have described clear changes in cortical and sub-cortical brain
structures which accompany normal aging. For example, in a recent study involving 148
healthy adults from 3 age groups (mean age 28 yrs.; 44 yrs.; 63 yrs.), Salat et al. (2009)
reported considerable regional changes in neural tissue properties with aging such as
decreased MR signal intensity from both gray and white matter and decreased cortical
thickness (Salat et al., 2009). To quantify within-subject changes in brain structure over
time, Raz et al. (2010) investigated brain region of interest (ROI) volume changes in a
population of middle-aged and older adults on 3 repeated MRI measures taken over a 30
month period (Raz et al., 2010). The authors noted that in healthy individuals, brain volume
is known to shrink significantly over relatively short time-periods, and with marked
individual variability in the rates of decline (Raz, et al., 2010). Interestingly, these studies
show that age-related decreases in cortical thickness appear to affect some cortical areas
more than others. For example, Raz et al. (2010) reported that the greatest mean 30-month
change was observed in the hippocampus whereas the pons did not change significantly over
this time. Salat et al. (2009) reported that cortical thickness decreased most significantly
with age in the superior frontal, precentral, postcentral, superior temporal, and occipital
regions and increased with age in the medial frontal regions. Currently, the mechanisms that
contribute to the changes in tissue properties and the functional and behavioral correlates of
age-related structural change remain unclear.

The purpose of the current study was to examine MEG gamma-band responses and MRI
measures of cortical thickness and volume in a population of participants over a broader
age-range (from 8 yrs to 46 yrs) and to directly assess the influence of the participant’s age
on these functional and structural brain measures. Currently, there are no studies comparing
visual gamma-band response over the life-span, particularly in children. However, previous
findings from adults (Muthukumaraswamy et al., 2010) predict that visual gamma-band
frequency will be inversely related to participant’s age. A subsidiary purpose, and notable feature of this paper, is that it represents the accumulated efforts of two MEG laboratories (CUBRIC and CHOP) with data pooled across international sites. While multi-centre studies are becoming increasingly common in large structural and functional MRI studies the current study represents (to our knowledge) the first demonstration of multi-centre data sharing across MEG centers.

Methods

This collaborative study involved the MEG lab at CUBRIC, Cardiff University, UK, and the Lurie Family Foundations MEG Imaging Center, at the Children’s Hospital of Philadelphia, USA. Nearly identical data collection methods, visual stimuli, and analysis methods were used, with analysis and results across sites pooled (all differences are noted in Methods).

Participants

One significant challenge embedded in life-span studies is to disentangle morphological and functional developmental change from the degenerative changes of late adulthood. Thus, by limiting inclusion of adults in our study up to 50 yrs. (mid-adulthood), we have attempted to limit the influence of degenerative processes affecting the structural and functional changes observed with normal aging.

Healthy adult (> 18 yrs) participants (CUBRIC; N=33, CHOP; N=13) ranged in age from 18.4 to 45.3 yrs. (mean age = 31.4 yrs). In addition healthy child participants (CHOP; N=13) ranged in age from 8.7 yrs to 15.6 yrs. All procedures were approved by the local ethics committee. Participants were fitted with three electromagnetic head coils (nasion and pre-auriculans) which were used for monitoring within-session head movement and for subsequent co-registration with each participant’s MRI.

MEG Hardware

Both CHOP and CUBRIC MEG laboratories use the CTF-Omega 275 channel radial gradiometer system (VSM MedTech). Whole-head MEG recordings were sampled at 1200 Hz (0–300 Hz band-pass). 3 sensors were turned off at CUBRIC due to excessive noise. Results from 31 adults participating at CUBRIC have been reported in a previously published manuscript (Muthukumaraswamy, et al., 2010).

MEG Recording Methods

**CUBRIC**—MEG/MRI fiducial coregistration at CUBRIC was performed by placing fiduciary markers at fixed distances from anatomical landmarks identifiable in participants’ anatomical MRIs (tragus, eye centre). Fiduciary locations were verified afterwards using high-resolution digital photographs.

Adult participants run at CHOP were volunteer researchers with previously acquired brain MRIs. For these participants, head surface and fiducial coil locations were digitized using Polhemus (Fastrak; Polhemus, USA). Fiducial coregistration was then based on in-house surface matching software which aligned the head surface extracted from each subject’s MRI with the Polhemus measured head shapes. As age-related MRI/MEG analyses were planned, we ensured that all participants MRI acquisitions occurred within 1 year of the MEG recording date.

Pediatric participants at CHOP were enrolled in on-going studies which included MRI structural scans recorded directly following the MEG recordings. For these participants,
MRI contrast markers were placed at MEG fiducial coil locations, prior to the MRI recordings, and were used for fiducial co-registration.

**Visual Stimuli**

These consisted of vertical, stationary, maximum contrast, three cycles per degree, square-wave gratings presented on a mean luminance background. Stimuli were presented in the lower left visual field and subtended 4° both horizontally and vertically, with the upper right corner of the stimulus located 0.5° horizontally and vertically from a small red fixation cross (Muthukumaraswamy et al., 2009). Participants were instructed to fixate and to press a response key with the right index finger at the termination of each stimulation period (varying in duration 1.5 to 2 s). To ensure that that participant attended to each trial, the response was required to occur within 700 ms in order for the next stimulus to occur. Failure to do so resulted in a prompt that the response was “too slow”. All stimulus presentations were controlled by Presentation software (Neurobehavioral Systems Inc). At CUBRIC stimuli were directly viewed on a Mitsubishi Diamond Pro 2070 monitor, with a screen size of 1024 by 768 pixels and a frame-rate of 100 Hz. The monitor was outside the magnetically shielded room and viewed directly from within, at 2.15 m, through a cut-away portal in the shield. At CHOP stimuli were presented through a back projection system via a Sanyo Protrax multiverse projector with a screen size of 1024 by 768 pixels and a frame rate of 60 Hz. A screen mounted phototransistor was used to synchronize MEG acquisition with actual time of delivery of visual stimuli, avoiding latency jitter due to refresh rate.

A pilot study was also conducted to assess the effect of background room luminance on our gamma-band measures. This test showed no significant differences were observed when running the visual contrast gratings experiment in low and bright levels of room luminance. Nevertheless, any potential differences in background room luminance between MEG laboratories were minimized by first ensuring that all stimuli were presented in a dimly lit MSR (confirmed with photographs). The results of the luminance pilot experiment can be found in Supplemental Material.

**MRI Methods**

**CUBRIC MRI** data were acquired on a 3 T General Electric HDx scanner using an eight channel receive only head RF coil (Medical Devices). A 3D Fast Spoiled Gradient Recalled (FSPGR) scan was obtained in an oblique-axial orientation, with maximum field of view = 256x256x192 and matrix = 256x256x192 to yield 1mm isotropic voxel resolution. (TR/TE = 7.9/3.0 ms; Inversion time = 450 ms; Flip angle = 20°).

**CHOP MRI** data were acquired on a 3T Siemens Verio (TM) scanner using a 32 channel receive only head RF coil. For each participant we obtained a 3D Magnetization-Prepared Rapid Acquisition Gradient-Echo (MP-RAGE) scan in an axial orientation, with field of view = 256x256x192 and matrix = 256x256x192 to yield 1mm isotropic voxel resolution. (TR/TE = 1900/2.87 ms; Inversion time = 1100 ms; Flip angle = 9°).

Cortical reconstruction and volumetric segmentation was performed with the Freesurfer image analysis suite, which is documented and freely available (http://surfer.nmr.mgh.harvard.edu/). The technical details of these procedures are described in prior publications (Dale, et al. 1999; Dale and Sereno 1993; Fischl and Dale 2000; Fischl, et al. 2004; Fischl, et al. 1999; Han, et al. 2006; Segonne, et al. 2004). Briefly, this processing includes removal of non-brain tissue using a hybrid watershed/surface deformation procedure (Segonne, et al. 2004), automated Talairach transformation, segmentation of the subcortical white matter and deep gray matter volumetric structures (including hippocampus, amygdala, caudate, putamen, ventricles) (Fischl, et al. 2002;
Fischl, et al. 2004) intensity normalization (Sled, et al. 1998), tessellation of the gray matter white matter boundary, automated topology correction (Fischl, et al. 2001; Segonne, et al. 2007), and surface deformation following intensity gradients to optimally place the gray/white and gray/cerebrospinal fluid borders at the location where the greatest shift in intensity defines the transition to the other tissue class (Dale, et al. 1999; Dale and Sereno 1993; Fischl and Dale 2000). Once the cortical model is created, the cerebral cortex is parcellated into units based on gyral and sulcal structure based on an existing atlas (Desikan, et al. 2006). The method uses both intensity and continuity information from the entire three dimensional MR volume in segmentation and deformation procedures to produce representations of cortical thickness, calculated as the closest distance from the gray/white boundary to the gray/CSF boundary at each vertex on the tessellated surface (Fischl and Dale 2000). The maps created use spatial intensity gradients across tissue classes and are therefore not simply reliant on absolute signal intensity. The maps produced are not restricted to the voxel resolution of the original data thus are capable of detecting submillimeter differences between groups. Procedures for the measurement of cortical thickness have been validated against histological analysis (Rosas, et al. 2002) and manual measurements (Kuperberg, et al. 2003; Salat, et al. 2004). Freesurfer morphometric procedures have been demonstrated to show good test-retest reliability across scanner manufacturers and across field strengths (Han, et al. 2006).

A large body of converging evidence exists from LFP (Gray and Singer 1989; Henrie and Shapley 2005; Logothetis et al., 2001) ECOG (Rols et al., 2001) and MEG studies (Hoogenboom et al., 2006; Muthukumaraswamy and Singh 2008) that the source of gamma-band activity in response to simple visual stimuli is from V1/V2. To reduce the number of statistical comparisons we therefore restricted our analysis of structural change to the relevant areas of the occipital lobe in this atlas; lingual, cuneal, and pericalcarine areas. Grey matter cortical reconstructions in these areas were assessed for 3 volumetric parameters (Volume, Surface Area and Cortical Thickness)

**SAM source localization**

MEG sources were localized using the differential SAM beamformer (Robinson and Vrba, 1999). Visual gamma-band (30-80 Hz) activity was localized using a 0.0 to 1.5 s (Active) and −1.5 to 0.0 s (Control) time windows obtained using covariance matrices band-pass filtered between 30 and 80 Hz. Peak locations of gamma-band activity were observed consistently in right hemisphere primary visual cortex. Each peak location was used to create source waveforms for time-frequency analysis. The beamformer weights vector for the peak location was explicitly computed (covariance calculated from −2 to 2 s; 30-80 Hz) and subsequently, the sensor data were projected through these weights to obtain a time varying estimate of the activity at the image peak location.

**Time-frequency analysis**

Time-frequency analysis assessed both induced and evoked responses from source waveforms using the Hilbert transform between 0 and 100 Hz at 0.5 Hz frequency step intervals, and represented as a percentage change from baseline values (−1.5 to 0 s) for each frequency band. Peak gamma-band frequency and amplitude measures (expressed in units of percent change from baseline) were obtained. Previous analysis and pilot recordings have shown that the gamma-band response from primary visual cortex exhibits both a “transient” component at stimulus onset (0 to ~ 0.3 s) as well as a “sustained” component that lasts for the duration of the grating stimulus. From the time-frequency spectrograms, we therefore calculated gamma-band frequency and amplitude measures for the transient and sustained response separately. A time window of 0 to 0.3 s was used to measure gamma-band transient frequency and amplitude, whereas the sustained response was measured using a 0.5 s to 1.5
s analysis window. Reported gamma-band frequency and amplitudes values were calculated by integrating +/- 5 Hz around the peak frequency observed in the average TFR for each peak location and was reported separately for both transient (0 to 0.3 s) and sustained (0.5 to 1.5 s) gamma-band time periods. Analysis of transient gamma-band responses was not performed in previous similar work (Muthukumaraswamy et al., 2010). An analysis of unbaselined gamma values (in nAm) can be found in Supplemental Material.

The Pearson product-moment correlation coefficient was used to assess linear associations between age and gamma band frequency and amplitude, as well as between age and volumetric parameters of the occipital lobe (noted above) extracted using FreeSurfer. Linear regression analyses were performed with SPSS (PASW Statistics v.18; http://www.spss.com)

**Results**

Source localized gamma-band differential SAM images are shown for four representative participants ranging in age from 8 - 46 yrs. in Figure 1. Consistent with previous reports using similar stimuli, gamma-band responses were observed in individuals to be localized near to the pericalcarine area (Adjamian et al., 2004; Brookes et al., 2005; Hall et al., 2005; Hoogenboom et al., 2006; Muthukumaraswamy and Singh 2008, Muthukumaraswamy et al., 2010; Swettenham et al., 2009). The extended area of source power change observed in these visual cortex responses is typical of power leakage from the SAM spatial filter, with the amount of leakage dependent on the SNR ratio, and the threshold applied (see Barnes and Hillebrandt (2003) for more detailed discussion relating to signal leakage in beamformer images).

Given the heterogenous nature of our participant population with respect to age we did not spatially normalize and average response locations. Time-frequency plots from early visual cortex peak locations show the characteristic *Transient* (0 - 0.3 s) and *Sustained* responses (0.5s - 1.5 s) to the presented visual stimulus. Given the temporal lag from stimulus onset, we interpret the Sustained response as exhibiting primarily induced rhythmic activity from visual cortex, whereas the Transient response analysis window spans a time period which includes the visual evoked-response to stimulus onset. Significant correlations were observed between Transient and Sustained gamma band Frequency ($R^2=0.65$; $(p<0.001)$ $y$(Transient)$=0.921x$(Sustained) + 10.108), and transient and sustained gamma band amplitude ($R^2=0.42$; $(p<0.001)$ $y$(Transient)$=1.067x$(Sustained) + 14.405).

Whereas each subject shows the transient and sustained gamma-band response, considerable inter-subject variability in gamma-band amplitude and frequency is observed (as reported previously by Swettenham et al., 2009; Muthukumaraswamy et al., 2009). In addition, young participants show the highest frequency gamma-band responses, whereas gamma-band power appeared unrelated to the participant’s age.

**Age vs. Gamma-band analysis**

Linear regression analysis was performed relating the participant’s age to gamma-band measures (Transient Gamma Peak Frequency; Sustained Gamma Peak Frequency). A significant negative correlation was observed for Age vs. Transient Response Peak Frequency ($R^2=0.37$, $p<0.001$). Similarly, a significant negative correlation was also observed for Age vs. Sustained Gamma Peak Frequency ($R^2=0.46$, $p<0.001$) (See Figure 2a and 2b). No significant Age vs. Gamma Amplitude (Transient or Sustained) correlation was observed. When just the CHOP data were analysed, similar transient frequency correlations ($R^2 = 0.73$ $p < 0.001$) and sustained frequency correlations ($R^2 = 0.58$ $p < 0.001$) were observed.
The mean peak frequency for the transient gamma was 58.62 Hz and for the sustained gamma was 52.65 Hz and these were highly correlated ($R^2 = 0.66$, $p < 0.001$). The mean change in transient gamma amplitude was 41.01 % and 24.93 % for sustained and these were also correlated ($R^2 = 0.42$, $p < 0.001$). Two sample paired t-tests of the mean peak frequency between transient and sustained gamma frequency was also significant (two tailed; $t(58) = -8.45$, $p < 0.001$).

**Age vs. Structural MR Analysis**

Linear regression analysis was conducted to assess the relationship between participant’s age and MRI based grey matter analysis from FreeSurfer. Linear regression analysis of MRI volumetric brain parameters from the Occipital lobe revealed a significant negative correlation for Age vs. Pericalcarine Thickness ($R^2 = 0.07$, $p<0.05$). Age vs. Cuneus Thickness also showed a significant negative correlation ($R^2 = 0.14$, $p<0.005$) as did Age vs. Cuneus Volume ($R^2 = 0.08$, $p<0.05$) (See Figure 3a and 3b).

Linear regression analysis was then conducted separately for the three significant occipital regions (Pericalcarine Thickness, Cuneus Thickness, and Cuneus Volume) in relation to transient and sustained gamma-band frequency measures. For Transient Gamma Peak Frequency, only the Cuneus Thickness linear regression approached significance ($R^2 = 0.05$, $p=0.08$). For Sustained Gamma Peak Frequency, a positive linear trend was observed between Pericalcarine Thickness ($R^2 = 0.06$, $p=0.06$). Cuneus Thickness correlated significantly with the Sustained Gamma Peak Frequency ($R^2 = 0.12$, $p<0.01$). Finally, Cuneus Volume was also significantly correlated with Sustained Gamma Peak Frequency ($R^2 = 0.13$, $p<0.005$). See Table 1 for a summary of all significant correlations observed between measures.

**Does Change in Cuneus Thickness or Cuneus Volume Explain the Decrease in Sustained Gamma Frequency with Age?**

Hierarchical regression analyses was performed to examined the unique influence of Age and Cuneus Thickness on Sustained Gamma Peak Frequency. The full regression model (Age and Cuneus Thickness) predicts 46.3% of the variance in Sustained Gamma Peak Frequency, $F(2,56) = 24.16$, $p < 0.001$. Added first, Age predicted 45.5% of the variance ($p < 0.001$). Including Cuneus Thickness explained a non-significant 0.8% of additional variance in the model for Sustained Gamma Peak Frequency and Age. When Cuneus Thickness was added to the model first it accounted for 11.5% of the variance in Sustained Gamma Frequency ($p < 0.01$), with Age accounting for an additional 34.8% of the variance ($p < 0.001$).

Hierarchical regression analyses was also performed to examined the unique influence of Age and Cuneus Volume on Sustained Gamma Peak Frequency. The full regression model (Age and Cuneus Volume) predicts 48.5% of the variance in Sustained Gamma Peak Frequency, $F(2,56) = 26.40$, $p < 0.001$. Added first, Age predicted 45.5% of the variance ($p < 0.001$). Including Cuneus Volume explained a non-significant 4% of additional variance in the model for Sustained Gamma Peak Frequency and Age. When Cuneus Volume was added first, it accounted for 13% of the variance in Sustained Gamma Frequency ($p < 0.001$), with Age accounting for an additional 35.5% of the variance.

For both models, Cuneus Thickness and Cuneus Volume do not significantly predict Sustained Gamma Peak Frequency after accounting for Age, thus the observed decrease in Sustained Gamma Peak Frequency with increasing age is not likely the result of decreased cortical thickness or cortical volume in visual areas. Rather Sustained Gamma Peak
Frequency, Cuneus Thickness and Cuneus Volume may be related indices of visual cortex maturation.

**Inter-laboratory Comparisons**

We performed post-hoc analyses to test for any potential inter-laboratory differences in our sample (CHOP n = 26, CUBRIC n = 33) for the variables of sustained gamma power and frequency as well as transient power and frequency. After controlling for age (as younger participants were collected at CHOP) no inter-laboratory differences were seen (all p > .05).

**Discussion**

A growing body of evidence suggests that synchronous gamma cortical oscillations are integral to variety of perceptual and cognitive functions (Fries 2009; Uhlhaas, et al. 2009; Uhlhaas, et al. 2010). However, less is currently known about how developmental and maturational changes affect gamma oscillations observed over the lifespan. The results from the current study show that contrast gratings-evoked gamma oscillation frequency decreases with age for both the *Transient* (0 to 0.3 s) and *Sustained* responses (0.5 - 1.5 s) to the presented visual stimulus. Previous research has related this transient period to input coming from the retina, through the LGN to cortex. This transient input from the retina may then initiate a sustained cortico-cortico gamma synchronization, which is generated and maintained exclusively in cortex (Castelo-Branco, et al., 1998). The precise and differential roles of these transient and sustained oscillations are not yet known, and the subject of some recent debate. Some have speculated that oscillations in the gamma range serve to maintain neural synchrony, enhancing the transmission and binding of information through visual cortex to higher-level areas (Singer W., 1999; Fries et al., 2001; Samonds and Bonds, 2005). Whereas the Sustained response window (0.5 1.5 s) likely represents a period dominated by induced cortical responses, the Transient response window (0 to 0.3 s) might capture both evoked and emitted components. However, both Transient and Sustained frequency and amplitudes were highly correlated indicating a tight functional relation. Thus, future studies might assess the degree to which these responses dissociate under varied stimulus conditions.

Cortical thickness and volume measures from occipital lobe, cuneus and pericalcarine cortex thickness was also observed to change with age. Whereas a significant correlation was observed between Cuneus Thickness and Gamma Sustained Peak Frequency and Cuneus Volume and Gamma Sustained Peak Frequency, results from hierarchical regression analysis showed participant’s age explained the vast majority of the decrease in Gamma Sustained Frequency regression model with age. Previous analyses of some of these data (Muthukumaraswamy et al 2010) showed only a correlation between pericalcarine cortex and gamma frequency (p < .05) while this is still marginally significant (p = .06) the inclusion of a younger participant pool has shown that neighbouring cuneus thickness and volume are also correlated with gamma frequencies. We thus interpret the differences between the current study and the Muthukumaraswamy et al., (2010) as related to the limited sampling of the age range in the adult study, which hampered uncovering age as a significant covariate in the relation between cuneus cortical thickness and GFP. In addition, we note that the neighbouring cuneal and pericalcarine thicknesses are quite strongly correlated ($r = 0.530, p < 1.60 \times 10^{-5}$). This suggests that both Gamma Frequency and Cuneus Thickness and Volume measures are sensitive to separate but related properties of age-dependant maturational change in visual cortex. These results are important as they show both functional and structural correlates of maturation are regionally specific, and may serve as an important metric of neural aging and age-associated neurological disease. Moreover, these changes may serve as indirect metrics of histological or pathological
processes and may be informative for understanding physiological processes of neural development, maturation, and age-related decline.

The current results raise two interesting questions: 1. what are the known anatomical, neurochemical and physiological changes which would produce a decrease in gamma-band frequency from primary visual cortex with increasing age? 2. What are the perceptual and behavioural correlates which can be associated with these structural and functional changes to the occipital lobe observed time?

1. How does the brain change structurally with age?

Maximal brain weight occurs at approximately 20 years of age, and declines at approximately 55 years of age (Dekaban, 1978). Conversely, white matter volume increases until approximately the mid-40s (Bartzokis et al., 2001; Sowell et al., 2003), which coincides with the peak myelination observed at approximately age 50 (Benes et al., 1994). Whereas the gross morphological structure (i.e., size) of the brain changes relatively little between childhood and mid-adulthood, dramatic changes to neural density and connectivity are known to be taking place over this time. These morphological changes are largely dominated by 2 main neurodevelopmental processes: synaptic pruning and myelination. In vivo volumetric studies show consistent and relatively linear decreases in gray matter density (an indirect MRI measure related to synaptic pruning) from a variety of cortical regions beginning in late childhood (Giedd et al., 1999; Sowell et al., 2002) and continuing relatively linearly through old age (Bartzokis et al., 2003; Courchesne et al., 2000; Ge, et al., 2002). During adolescence, frontal and parietal lobes show highly significant increases in white matter along with concomitant decreases in gray matter (Giedd et al., 1999; Sowell et al., 2002). Grey matter density reduction over the childhood to adult range appears to show acceleration in the post-adolescent age range, mostly in the dorsal frontal cortices (Sowell et al., 2003; Sowell et al., 2001). These results suggest that changes in gray matter density between childhood and young adulthood may index maturation dependent increases in computational demands as frontal lobe executive functions develop in adolescence, and thus are not changing at the same rates over lifespan. Of note, the clear decrease in gray matter density from dorsal frontal areas over the 10 - 40 yr. range appears to remain relatively constant in density after -50 yrs. (Sowell et al., 2003). In addition to synaptic density, age-dependent neurochemical processes are also known to change with development and maturation (Jansen et al., 2010).

Neurochemistry underlying brain development and maturation

Gamma-band responses and long-range synchronization in neocortex are thought to be governed principally by GABAergic interneurons (Frankle et al. 2009; Uhlhaas et al., 2009; Uhlhaas et al., 2010). These neocortical interneurons use the inhibitory neurotransmitter γ (gamma)-aminobutyric acid (GABA) to dampen cortical activity by increasing chloride (Cl−) conductance producing membrane hyperpolarization and decreased excitability. In children and adults, GABA mediates the majority of fast inhibitory neurotransmission in the central nervous system through its activation of the GABAA receptor. However, both the subunit composition neuronal GABA receptors and functional role changes during prenatal and postnatal development in humans (Andersen et al., 2002; Brooks-Kayal and Pritchett 1993; Kanaumi, et al., 2006; Reichelt et al., 1991). Due to elevated intracellular Cl-concentrations in immature neurons, GABA signaling in neonatal brain acts as an excitatory neurotransmitter – which switches to an inhibitory neurotransmitter after about the first 2 years of life (Jansen et al., 2010). In addition, GABA receptor α1 and γ 2 subunit expression are known to increase over the first 5–6 years of life before reaching a plateau, whereas α4 subunit expression decreases during this same time period (Jansen, et al. 2010). It is currently not clear how changes in receptor density correlate with gross non-invasive
GABA measures such as non-invasive Magnetic Resonance Spectroscopy (MRS). However, widespread decreases in MRS GABA concentration with age have been reported to correlate negatively with normal aging, in areas such as dorso-lateral prefrontal cortex (DLPFC), orbito frontal cortex (OFC) and sensorimotor cortex (SMC) (Grachev and Apkarian 2001), as well as visual cortex (Bigal et al., 2008). More recently, a positive correlation was observed between MRS resting endogenous GABA concentration in medial occipital cortex and gratings-induced gamma frequency (Muthukumaraswamy et al., 2009). Similar recent findings have also been observed between MRS resting endogenous GABA concentration and movement-related gamma synchrony in motor cortex (Gaetz et al., 2011). Thus, the age-related decreases in gamma frequency observed in the current study may index age-related decreases in MRS GABA concentration, or both gamma-band frequency and GABA concentration may be sensitive to some additional and related processes of brain maturation.

**Perceptual and behavioural correlates of visual cortex maturation**

If, as we speculate above, age-related changes in gamma-band frequency are related to changes in the cortical excitation/inhibition balance then we might well predict age-related changes in gamma frequency to be correlated with performance on tasks that are thought to be dependent on GABAergic inhibition. The most compelling case for this is orientation discrimination, where animal neurophysiology has shown that intracortical inhibition sharpens neuronal orientation selectivity (Shapley, Hawken and Ringach, 2003). When GABA is blocked by antagonists, neural orientation tuning is broadened or even abolished (Sillito, 1975) while the addition of GABA to aged cells restores their orientation tuning (Leventhal et al., 2003). Using MEG and MRS in humans we recently demonstrated that orientation discrimination performance was predicted by both occipital GABA concentration and gamma-band frequency within the same area - suggesting that variability of GABAergic inhibition can indeed lead to variability in human performance (Edden et al., 2009). On other tasks, it has been shown that older subjects are actually better than younger subjects at discriminating brief, large-field, motion stimuli (Tadin et al., 2003) – a counterintuitive finding that has been linked to reduced GABAergic inhibition in the older cohort, leading to reduced centre-surround suppression. To date, an explicit link between age-related performance changes and age-related changes in GABA has not been made experimentally. Furthermore, to our knowledge, performance changes on these tasks through the early years of development, when the GABA system is maturing, have not been investigated.

**Conclusion**

To our knowledge, this study is the first published multicenter MEG study. With this work, we have employed nearly identical methods between two research centers, and replicated previously published research findings (Muthukumaraswamy et al, 2010) using an independent sample of adults (CHOP vs. CUBRIC). Moreover, we have extended this observation to healthy population of adolescents and children. This collaborative approach to the study of developmental neuroscience represents a more efficient and statistically powerful path to scientific discovery, particularly when relatively large samples of participants are needed.

Our work has several important implications for basic and developmental neuroscience. Studies aimed at addressing the functional significance of cortical oscillations should control for maturational processes which may directly affect the frequency of the observed cortical oscillations. Future work designed to relate perceptual and behavioural consequences of this decrease in gamma-band frequency may be important for explaining how gamma-band oscillations contribute to V1 function. In addition, it is clear that age-related changes in cortical thickness affect some cortical areas more than others, yet the reason for this, and the perceptual and behavioural consequence of this change remain unclear. Overall, these
morphological and functional changes with maturation appear to be regionally specific, and may thus be informative for understanding physiological processes of neural development, maturation, and age-related decline.

**Supplementary Material**

Refer to Web version on PubMed Central for supplementary material.

**Acknowledgments**

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**References**


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Figure 1.
Source localized gamma-band differential SAM images are shown on the left for 4 representative participants of varying age. The peak location for each source localisation image is indicated by the green dot in each MRI image. Time-frequency plots from peak locations and gamma-band amplitude plots are shown to the right. Inter-subject variability in gamma-band amplitude is observed (as reported previously (Muthukumaraswamy et al., 2009)). Peak amplitude gamma-band frequency for both the Transient (0 to 0.3 s) Gamma frequency as well as Sustained (0.5 to 1.5 s) gamma frequency appears to decreases with increasing age. The red * represents the reported peak frequency.
A significant negative correlation was observed between the participant’s age and the transient gamma-band peak frequency ($R^2 = 0.37$, $p < 0.001$). 2b shows the significant negative correlation between the participant’s age and sustained gamma-band peak frequency ($R^2 = 0.46$, $p < 0.001$). No significant differences were observed between the slopes of these regression lines, thus the correlation and regression equation reported is for all participants (N=59).
A significant negative correlation was observed between participant’s age and cuneus thickness ($R^2 = 0.14$, $p < 0.005$), and a near-significant negative correlation was observed between participant’s age and pericalcarine thickness ($R^2 = 0.07$, $p = 0.06$). 3b shows the significant positive correlation observed between participant’s age and cuneus volume ($R^2 = 0.08$, $p < 0.05$).
Table 1

Summary Table of Correlation Results.

<table>
<thead>
<tr>
<th></th>
<th>Age</th>
<th>Transient Gamma (0 to 0.3 s)</th>
<th>Sustained Gamma (0.5 to 1.5 s)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Hz</td>
<td>Power</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td>R²=0.37; p&lt;0.000</td>
<td>n.s.</td>
</tr>
<tr>
<td>Peri-Calcarine</td>
<td>Thickness (mm)</td>
<td>R²=0.067; p=0.049</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>Surface Area (mm²)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>Volume (mm³)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cuneus</td>
<td>Thickness (mm)</td>
<td>R²=0.142; p=0.003</td>
<td>R²=0.054; p=0.078</td>
</tr>
<tr>
<td></td>
<td>Surface Area (mm²)</td>
<td>n.s.</td>
<td>n.s.</td>
</tr>
<tr>
<td></td>
<td>Volume (mm³)</td>
<td>R²=0.082; p=0.028</td>
<td>n.s.</td>
</tr>
</tbody>
</table>