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V1 surface size predicts GABA concentration in medial occipital cortex

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ABSTRACT

A number of recent studies have established a link between behavior and the anatomy of the primary visual cortex (V1). However, one often-raised criticism has been that these studies provide little insight into the mechanisms of the observed relationships. As inhibitory neural interactions have been postulated as an important mechanism for those behaviors related to V1 anatomy, we measured the concentration of inhibitory gamma-amino butyric acid (GABA) in the medial occipital cortex where V1 is located using magnetic resonance spectroscopy (MRS) and estimated the surface area of V1 using fMRI retinotopic mapping. We found a significant positive relationship between GABA concentration and V1 surface area. This relationship was present irrespective of whether the MRS voxel had a fixed size across participants or was proportionally sized to each individual's V1 surface area. Hence, individuals with a larger V1 had a higher GABA concentration in the medial occipital cortex. By tying together V1 size and GABA concentration, our findings point towards individual differences in the level of neural inhibition that might partially mediate the relationships between behavior and V1 neuroanatomy. In addition, they illustrate how stable microscopic properties of neural activity and function are reflected in macro-measures of V1 structure.

Introduction

Human V1 surface area and volume show interindividual variation up to a factor of four (Andrews et al., 1997; Filimonov, 1932; Stensaas et al., 1974) and have a strong hereditary component (Bakken et al., 2012; Chen et al., 2012; Panizzon et al., 2009; Wierenga et al., 2014; Winkler et al., 2010).

Researchers have recently begun to investigate the relationship between primary visual cortex (V1) anatomy and behavior. These studies found that a larger V1 surface size is linked to higher sensitivity for spatial orientation (Song et al., 2013) and location (Song et al., 2015), decreased speed of binocular rivalry-induced perceptual waves (Genç et al., 2013), and a lower susceptibility to contextual visual illusions (Schwarzkopf and Rees, 2013; Schwarzkopf et al., 2011; Song et al., 2013). In addition, more recent studies show that not only perceptual properties, but also higher cognitive functions with a close link to vision, such as visual working memory (Bergmann et al., 2014), mental imagery (Bergmann et al., 2015) and attention (Verghese et al., 2014), exhibit significant relationships with V1 size. Again, a larger V1 is associated with better behavioral performance, i.e., increased visual working memory storage, higher imagery precision and higher attentional abilities.

However, one common criticism of the studies linking V1 size to behavior is that they provide little direct information about the mechanisms that mediate the observed relationships. Inhibitory interactions have been proposed as a potential mechanism for those behaviors (Edden et al., 2009; Kang et al., 2010; Li et al., 2008; Wang, 2001; Wilson et al., 2001).

Results from previous research hint at a potential link between the inhibitory neurotransmitter GABA and V1 size: GABA has been shown to correlate positively with individual gamma peak frequency (Edden et al., 2009; Muthukumaraswamy et al., 2009; but see Cousijn et al., 2014). This is the frequency at which the power of visually induced oscillations in the gamma band (30–80Hz) is highest compared to baseline conditions (Henrie and Shapley, 2005). Gamma peak frequency, on the other hand, correlates positively with V1 surface area (Schwarzkopf et al., 2012) and individual sensitivity for spatial orientation (Edden et al., 2009).

As a proxy for cortical inhibition, we determined the concentrations of gamma-amino butyric acid (GABA) using magnetic resonance

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spectroscopy (MRS). In addition, we also determined the concentrations of Glx—the composite measure of glutamate and glutamine—to evaluate the specificity of the relationship between GABA and anatomy. Two MRS measurements were conducted in each participant: in the first measurement, the MRS voxel had a fixed size in all participants; in the second measurement, the MRS voxel was proportional to each individual's V1 surface size. The MRS voxels were positioned in the human medial occipital cortex, which is the cortical region where V1 is located. The concentrations of GABA and Glx and their ratio were then related to early visual cortex anatomy, which was mapped using conventional fMRI retinotopic mapping procedures. In addition, V1 was also mapped anatomically using a surface-based probabilistic method (Hinds et al., 2008). Based on the prior data, we hypothesized that a larger V1 would be associated with a higher medial occipital concentration of GABA.

Materials and methods

Participants

Twenty-one participants aged between 18 and 36 years were recruited for the study (median: 26 years; 9 males). All participants were right-handed and had normal or corrected-to-normal vision. None of them had a history of psychiatric or neurological disorders. The participants were paid for participation. Written informed consent was obtained from all participants and the ethics committee of the Max Planck Society approved the study.

Neuroimaging experiments

All imaging data were acquired at the Brain Imaging Center Frankfurt am Main, Germany. The scanner used was a Siemens 3-T Trio (Siemens, Erlangen, Germany) with a maximum gradient strength of 40 mT/m. Imaging measurements were carried out in two sessions.

Anatomical imaging 1. In the fMRI retinotopic mapping scan sessions, an eight-channel head coil was used. For anatomical localization and coregistration of the functional data, T1-weighted anatomical images were acquired first using a sagittal-oriented magnetization-prepared rapid gradient echo (MP-RAGE) sequence with the following parameters: TR = 2250 ms; TE = 2.6 ms; flip angle: 9°, FoV: 256 mm; resolution = $1 \times 1 \times 1$ mm^3).

Anatomical imaging 2. Prior to the MRS measurements, which were done using a transmit/receive head coil and a maximum gradient strength of 40 mT/m, a sagittal-oriented magnetization-prepared rapid gradient echo (MP-RAGE) scan was recorded (TR = 1600 ms; TE = 2.59 ms; flip angle: 9°; FoV: 250 mm, resolution = $1 \times 1 \times 1$ mm^3). To further improve the positioning of the MRS volumes of interest, a short T2 scan oriented along the axis of the calcarine sulcus was added (TR = 3140 ms; TE = 10.7 ms; slice thickness: 6 mm; acquisition time: 1:23 min). The vbm5 extension of SPM5 was used to segment the T1 anatomical scans of the MRS session into gray and white matter (http://www.fil.ion.ucl.ac.uk/spm/). The segmented data was used to retrieve information about the GM/WM proportion in the MRS voxel.

fMRI retinotopic mapping measurement and analysis

This procedure has already been described in previous studies (see Bergmann et al., 2014; Bergmann et al., 2015; Genç et al., 2013). A gradient-recalled echo-planar (EPI) sequence with the following parameter settings was applied: 33 slices, TR = 2000 ms, TE = 30 ms, flip angle = 90°, FoV = 192 mm, slice thickness = 3 mm, gap thickness = 0.3 mm, resolution = $3 \times 3 \times 3$ mm^3. An MR-compatible goggle system with two organic light-emitting-diode displays was used for presentation of the stimuli (MR Vision 2000; Resonance Technology Northridge, CA), which were generated with a custom-made program based on the Microsoft DirectX library (Muckli et al., 2005). The maximal visual field subtended 24° vertically and 30° horizontally.

Retinotopic mapping procedure. To map early visual cortices V1, V2 and V3, our participants completed two runs, a polar angle and an eccentricity mapping run. The rationale of this approach has already been described elsewhere (e.g. Sereno et al., 1995; Wandell et al., 2007). Polar angle mapping: For the mapping of boundaries between areas, participants were presented with a black and white checkerboard wedge (22.5° wide, extending 15° in the periphery) that slowly rotated clockwise around the fixation point in front of a gray background. In cycles of 64 s, it circled around the fixation point 12 times at a speed of 11.25 in polar angle/volume (2 s). Eccentricity mapping: To map bands of eccentricity on the cortical surface to the corresponding visual angles from the center of gaze, our participants were presented with a slowly expanding flickering black and white checkerboard ring in front of a gray background (flicker rate: 4 Hz). The ring started with a radius of 1° and increased up to a radius of 15°. The expansion cycle was repeated seven times, each cycle lasting 64 s. The participants' task in both mapping experiments was to maintain central fixation.

Retinotopic mapping data analysis. We used FreeSurfer's surface-based methods for cortical surface reconstruction from the T1-weighted image of each participant (http://surfer.nmr.mgh.harvard.edu/fswiki/RecommendedReconstruction; Dale et al., 1999; Fischl et al., 1999b). FSFAST was applied for slice time correction, motion correction and co-registration of the functional data to the T1-weighted anatomical image. Data from the polar angle and eccentricity mapping experiment were analyzed by applying a Fourier transform to each voxel's fMRI time series to extract amplitude and phase at stimulation frequency. Color-encoded F-statistic maps were then computed, each color representing a response phase whose intensity is an F-ratio of the squared amplitude of the response at stimulus frequency divided by the averaged squared amplitudes at all other frequencies (with the exception of higher harmonics of the stimulus frequency and low frequency signals). The maps were then displayed on the cortical surface of the T1-weighted image. Boundaries of areas V1, V2 and V3 were then estimated manually for each participant by two independent raters (the first and third author) based on the phase-encoded retinotopic maps up to an eccentricity of 7.2°, which is among the eccentricities that have been typically used to map central early visual cortex in previous studies on the relationship between individual neuroanatomy and behavior or other cortical measures (Bergmann et al., 2014, 2015; Schwarzkopf and Rees, 2013; Schwarzkopf et al., 2011, 2012; Song et al., 2013, 2015). Inter-rater reliability of early visual cortex' surface size and cortical thickness showed high concordance between the two raters' judgments of V1 and V2 (V1 surface: $r = .908$, $p < .001$; V1 volume: $r = .907$, $p < .001$; V1 thickness: $r = .966$, $p < .001$, V2 surface: $r = .900$, $p < .001$; V2 volume: $r = .846$, $p < .001$.; V2 thickness: $r = .966$, $p < .001$). In V3, the agreement between the two raters was lower for surface and volume ($r = .474$, $p = .030$; V3 volume: $r = .576$, $p = .006$), but remained high for thickness ($r = .950$, $p < .001$). The values of the two ratings were then averaged for further analyses.

Anatomical parcellation of V1. Apart from estimating the boundaries of the early visual cortex functionally, we used Freesurfer's surface-based probabilistic method to predict V1 boundaries in each participant individually (Hinds et al., 2008). In contrast to the fMRI retinotopic mapping approach, which only captures the more central parts of V1, the surface-based prediction method based on anatomical landmarks aims to measure the area of V1 in its entirety. To reduce bias, a highly conservative threshold of 0.8 was used, which is the probability that a vertex lies within the actual boundary of V1. Again, volume, surface and thickness of overall aV1 were determined and related to behavior.

Gray matter volume analysis of the whole cortex. We also used the surface-based analysis approach to derive morphometric measures of the whole brain using FreeSurfer's Qdec application. After the earlier described preprocessing of the anatomical data, the surface, thickness, and curvature data were smoothed using a full width at half maximum Gaussian filter of 10 mm. A surface-based spatial normalization step was then used for group alignment, which consisted of a transformation of each individual surface into its spherical representation and then a non-rigid adjustment of the representation to a common-space spherical surface (fsaverage) according to the folding patterns (Fischl et al., 1999a). Following this step, the volume data of each individual were applied to the common group space, which allowed for cortical volume comparisons at homologous points within the brain. Vertex-wise correlations with medial occipital neurotransmitter concentrations were computed. The results were tested using a pre-cached Monte Carlo Null-Z simulation with 10,000 iterations and a cluster-wise probability threshold of $p < 0.05$ to correct for multiple comparisons (Hagler et al., 2006).

MRS measurements and data analysis

GABA measurement and data analysis. Estimates of medial occipital GABA and Glx concentrations were obtained from two measurements: In the first measurement, GABA-edited MR spectra were acquired from a $2.5 \times 2.5 \times 4\ cm^3$ volume positioned in the medial occipital lobe (see Fig. 1A) using the GABA specific sequence of the MEGA-PRESS method (Edden and Barker, 2007; Mescher et al., 1998; Mullins et al., 2014). In the second measurement, we acquired GABA-edited MR spectra from a volume in the medial occipital cortex that was proportional to the surface area of central V1 of each individual. Accordingly, the MRS voxel had a volume of $1.7 \times 2 \times 4\ cm^3$ in the participant with the smallest central V1 surface ($740.5\ mm^2$); in the other participants, the voxel's size was scaled proportionally with the individual's surface size of functional (i.e. fMRI retinotopically mapped) V1. By doing so, we attempted to rule out potential confounds that might arise from the MRS voxel overlapping with other surrounding areas to a varying degree depending on V1 size (Hendry et al., 1987; Zilles et al., 2002); however, this measurement also entails several complications: first, the level of noise, which is lower with a larger MRS voxel and thus results in largely differing noise levels between individuals, and second, the positioning of the voxel, which may vary largely between participants: as the MRS voxel has to be positioned at a considerable distance from the calotte to avoid disruptive noise from fat molecules (Backens, 2010), the bigger voxels in participants with a larger V1 may encompass much larger proportions of other regions not of interest, compared to the smaller voxels in individuals with a smaller V1. In one participant (S1), this had the effect that the MRS voxel could not be positioned in medial occipital cortex, and thus S1 had to be excluded from further analysis.

We custom-scaled the MRS voxel proportionally to central V1 surface size and not volume, as our prior hypothesis regarded the relationship between V1 surface size and GABA concentration, not volume. Nevertheless, V1 surface size and volume were almost perfectly correlated in our sample ($r = .918$, $p < .001$), hence MRS voxel sizes would have been very similar had they been scaled to V1 volume instead of surface size. Furthermore, due to the high convergence of the results with different MRS voxel sizes (see Results) it is unlikely that scaling to V1 volume instead of surface size would have made a difference to the results.

Experimental settings for both MRS measurements were as follows: TR = 1500 ms, TE = 68 ms; a Gaussian editing pulse was applied at −1.9 ppm (odd) and −4.1 ppm (even) in alternate scans. 256 scans were collected in 6:30 min.

MRS spectra were analyzed with jMRUI v.4.0 (http://www.mrui.uab.es/mrui/mrui_Overview.shtml), which estimated the best fit of the spectra using AMARES. A Henkel-Lanczos Singular Value Decomposition (HLSVD) filter was employed to remove the residual water signal

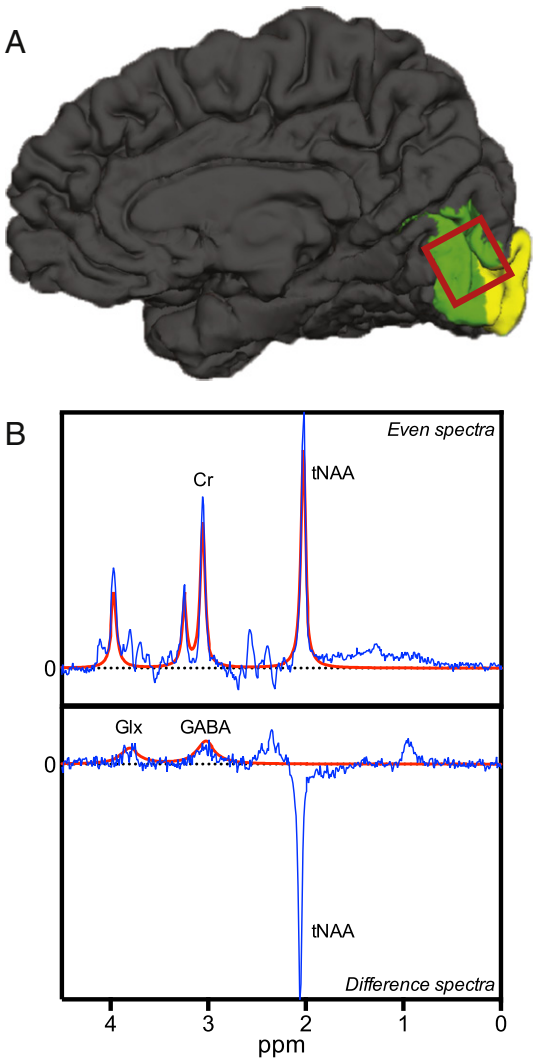

Fig. 1. MR spectroscopy voxel location and example spectrograms. **A.** Positioning of the single GABA voxel (red square) in the medial occipital lobe. Yellow indicates the location of the functionally defined central V1, which represents the central visual field up to an eccentricity of 7.2°. Green indicates the region of V1 that is additionally captured by the anatomical estimation of overall aV1 size (Hinds et al., 2008). As illustrated, the anatomical estimation of the boundaries of overall aV1, which aims to measure V1 in its entirety, covers a substantially larger part of the medial occipital cortex. The size of both anatomically and functionally estimated V1 varied strongly between participants. **B.** Example GABA spectra obtained from the single voxel shown in **A**. The blue line represents the measurement data, the red line the best fit. Peaks of the main metabolites are indicated. GABA levels were determined by subtracting the spectra of the even scans from those of the odd scans and normalizing the signal intensity using either the total NAA (tNAA) or creatine (Cr) signal intensity as a reference.

from the even free induction decay (FID) spectra before quantifying creatine (Cr), choline (Cho) and a cumulative signal representing *N*-acetyl-aspartate and *N*-acetyl-aspartyl-glutamate (total NAA or tNAA). The time domain fit was performed with an exponentially decaying sinusoidal function (Lorentzian) with fixed frequencies relative to Cr at 3.05 ppm. GABA and the cumulative signal of glutamine and glutamate (Glx) were quantified from the difference spectra, which result from the subtraction of the even scans from the odd scans (see Fig. 1B). GABA and Glx signal intensity was determined by a fit in the time domain using Lorentzian line shape at a fixed linewidth of 25 Hz. The zero-order phase was set to the value obtained from the analysis of the even data. The GABA and Glx signal intensities of each individual participant were then normalized to the signal intensity of tNAA in the voxel. As an additional parameter, we also computed GABA levels using the signal intensity of Cr as a reference. The GABA and Glx levels obtained by this

procedure are considered to reflect concentration *differences* between different subjects, which is based on the assumption that neither tNAA nor Cr concentrations as well as their MR relaxation parameters (T1 and T2) vary in the targeted brain regions. The estimation of *absolute* concentrations would require further calibrations correcting for partial saturation (T1), dephasing (T2), and editing efficacy.

Since voxel-averaged metabolite concentrations depend on the partial volume of gray matter (GM) and white matter (WM), the GM proportion within the voxel was computed as the ratio between the voxel's GM proportion and the sum of the GM and WM proportion (GM/(GM + WM)).

Statistical analyses

All data sets were first checked for normality using the Shapiro–Wilk normality test. None of them showed a violation of the normal distribution assumption. Statistical analyses consisted of multiple linear regression analyses and Pearson product moment correlations, which were tested two-sided.

Results

We first analyzed the relationships between individual V1 anatomy and GABA concentrations determined from an equally sized voxel ($2.5 \times 2.5 \times 4\ cm^3$) in the medial occipital cortex using the GABA specific sequence of the MEGA-PRESS method (see Materials and Methods and Fig. 1A and B). In accordance with our hypothesis, we found a significant positive relationship between fMRI retinotopically mapped central V1 surface size and GABA levels ($r = .455$, $p = .038$, see Fig. 2 and Table 1, first row). There was no relationship with V1 thickness ($r = -.034$, $p = .882$), and the relationship between GABA and central V1 volume (which is the combination of surface area and thickness) only trended towards significance ($r = .391$, $p = .08$). In exploratory analyses, no significant relationships were found with V2 anatomy (all $p > .232$). In V3, both volume and thickness fell short of significance (V3 volume: $r = .407$, $p = .067$, V3 thickness: $r = .390$, $p = .081$), and there was no relationship with V3 surface area ($r = .178$, $p = .440$).

Next we examined the relationships between GABA and anatomically defined primary visual cortex (aV1). In contrast to fMRI retinotopic mapping, this probabilistic method aims to measure V1 in its entirety (Hinds et al., 2008; see Materials and Methods). We found significant relationships between individual overall aV1 volume and GABA levels ($r = .479$, $p = .028$, see Fig. 3), and overall aV1 thickness and GABA levels ($r = .444$, $p = .044$). However, there was no significant relationship with overall aV1 surface area ($r = .248$, $p = .278$).

To assess the specificity of our results, we then looked at the relationship between early visual cortex anatomy and the concentration of Glx. In contrast to GABA, there was no relationship with V1 surface size ($r = .075$, $p = .747$). When computing a multiple linear regression analysis with V1 surface size as dependent and Glx and GABA concentration as independent variables, only GABA contributed significantly to the prediction of V1 size ($beta = .511$, $t(20) = 2.239$, $p = .038$), whereas Glx did not ($beta = -.139$, $t(20) = -.595$, $p = .559$). In addition, with the exception of V3 thickness, none of the other anatomical parameters of early visual cortex showed significant relationships with the concentration of Glx (see Table 2, first row).

We used parametric Pearson product moment correlation to compute the strength of linear relationships, as the statistical preconditions to do this were met (see Methods). However, due to the nature of our measures, with areal or volumetric measures on the one hand and (linear) neurotransmitter concentrations on the other hand, it is possible that non-linear relationships exist that remained undetected or underestimated in linear analyses. For this reason, we also examined the relationship between V1 anatomy and GABA concentration using non-parametric Spearman rank correlations. The results were strongly convergent with those of the linear analyses: replicating the previous

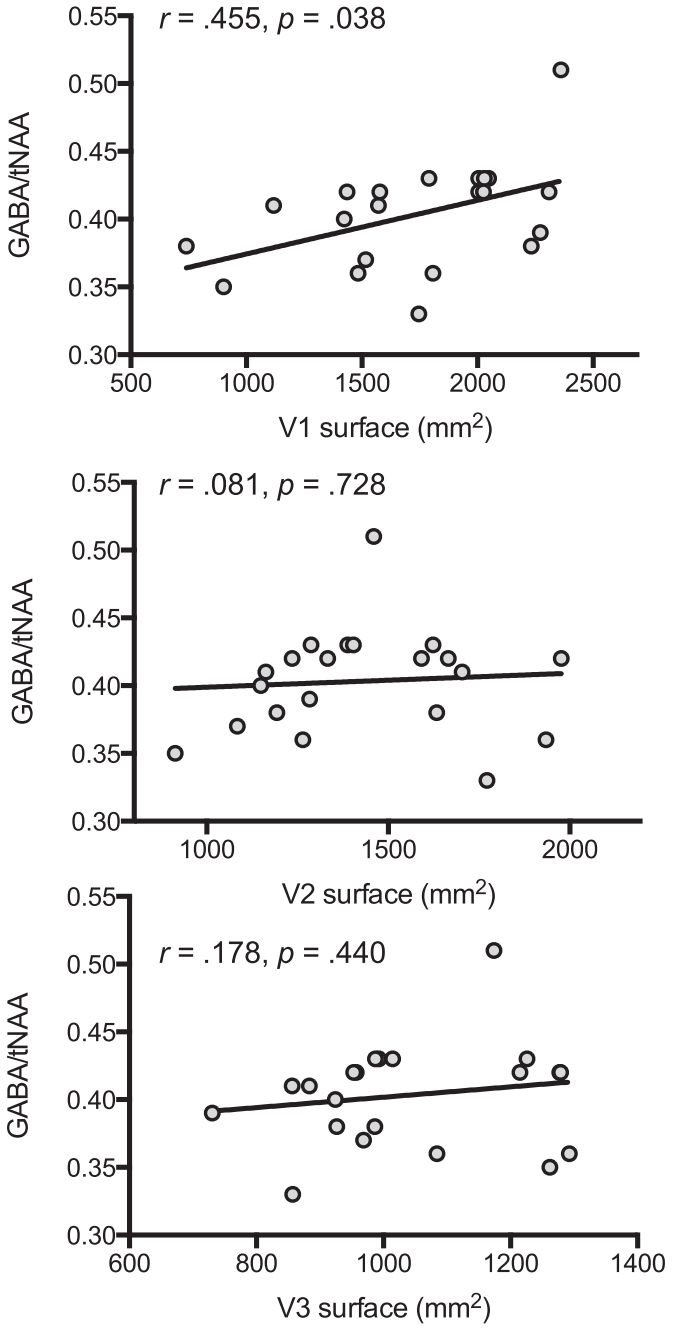

Fig. 2. Central V1–V3 surface sizes and their relationship to GABA concentration in medial occipital cortex. Each data point indicates the values of one individual, while the line represents the linear regression estimate. Bivariate correlation coefficients and the corresponding significance levels are included in each plot. Individual GABA level was significantly predicted by V1 surface size: individuals with a larger V1 tended to have higher levels of the inhibitory neurotransmitter in this region. No significant correlations were found with V2 or V3 surface size.

results, we found a significantly positive correlation between V1 surface size and GABA concentration ($r_s = .487$, $p = .025$). This time, the positive correlation with V1 volume also reached statistical significance ($r_s = .463$, $p = .034$), while V1 cortical thickness was again non-significant ($r_s = .005$, $p = .982$). No significant relationships were found between the concentration of GABA and the anatomy of V2 and V3 (all $p > .062$). In contrast to the linear relationships, however, the non-parametric relationships between GABA concentration and anatomically mapped aV1 were non-significant (all $p > .077$). In addition, there were again no significant relationships between the concentration of Glx and V1 anatomy (all $p > .51$).

Table 1
Statistical relationships between neurotransmitter concentrations in medial occipital cortex and measures of early visual cortex anatomy.

	GABA			
	Equally sized MRS voxel (GABA/tNAA)	Equally sized voxel (GABA/Cr)	Equally sized MRS voxel—males only ($N = 9$) (GABA/tNAA)	Proportional MRS voxel ($N = 20$) (GABA/tNAA)
V1 volume	.391 (.08)	.363 (.106)	.540 (.133)	.438 (.053)
V1 surface size	**.455 (.038)**	**.492 (.024)**	**.764 (.017)**	**.453 (.045)**
V1 cortical thickness	−.034 (.882)	−.174 (.451)	−.158 (.684)	.029 (.903)
V2 volume	.240 (.295)	.354 (.115)	.311 (.415)	.162 (.495)
V2 surface size	.081 (.728)	.201 (.383)	.229 (.554)	−.058 (.808)
V2 cortical thickness	.272 (.233)	.241 (.292)	.543 (.131)	.434 (.056)
V3 volume	.407 (.067)	**.485 (.026)**	.198 (.610)	.128 (.590)
V3 surface size	.178 (.440)	.271 (.235)	−.135 (.728)	−.094 (.694)
V3 cortical thickness	.390 (.081)	.389 (.081)	.269 (.484)	.395 (.085)
aV1 volume	**.479 (.028)**	**.540 (.011)**	**.826 (.006)**	.299 (.200)
aV1 surface size	.248 (.278)	.383 (.087)	.595 (.091)	.111 (.640)
aV1 cortical thickness	**.444 (.044)**	.369 (.10)	.614 (.078)	.389 (.09)

Note: The values indicate bivariate correlations, the *p*-values in brackets their respective significance levels. Significant correlations ($p < .05$) are written in bold. Please note that no multiple comparison correction was conducted due to the existence of specific prior hypotheses about the relationship between GABA concentration and V1 anatomy. Abbreviations: aV1 = anatomically estimated (i.e. overall) V1 (Hinds et al., 2008).

As it is plausible that neurotransmitters are mainly found in gray matter, we additionally checked whether the significant relationships between V1 anatomy and GABA were not merely due to differences in the individual gray matter proportion within the MRS voxel. For this purpose, we computed a multiple linear regression analysis using GABA concentration as a dependent variable and central V1 surface size and the MRS voxel's gray matter proportion as independent variable. However, only central V1 surface size contributed significantly to the prediction of GABA levels ($beta = .490$, $t(20) = 2.153$, $p = .045$), whereas the MRS voxel's gray matter proportion did not ($beta = -.088$, $t(20) = -.387$, $p = .703$).

A similar pattern emerged when we computed analogous multiple linear regression analyses for overall aV1 volume/thickness, using GABA concentration as a dependent variable and overall aV1 volume/thickness and the MRS voxel's gray matter proportion as independent variable: Again, aV1 volume showed a significant contribution to the prediction of GABA concentration ($beta = .476$, $t(20) = 2.258$, $p = .037$), whereas the voxel's gray matter proportion had none ($beta = .012$, $t(20) = 0.055$, $p = .957$); the contribution of aV1 thickness failed significance ($beta = .444$, $t(20) = 2.044$, $p = .056$), whereas there was again no contribution of the voxel's gray matter proportion ($beta = .00$, $t(20) = 0.00$, $p = 1.0$).

In our analyses, we used the intensity of the cumulative signal of *N*-acetylaspartate and *N*-acetylaspartylglutamate (tNAA) to normalize the GABA signal intensity within each individual. These GABA levels refer to the standard metabolites commonly used (Mullins et al., 2014). However, some studies instead use creatine (Cr) as a reference. We therefore recomputed the correlations with V1 anatomy using GABA/Cr instead of GABA/tNAA. The analysis yielded a similar pattern of results (see Table 1, second row).

Furthermore, most MRS studies only use male participants due to concerns regarding the variability of GABA levels over the menstrual cycle in females (Epperson et al., 2002; Harada et al., 2011). For this reason, we also analyzed our data using only the male participants from our sample. Despite the reduced statistical power for the much lower sample size ($N = 9$), we again found a highly similar pattern of significant results (see Table 1, third row).

We next analyzed the relationship between GABA levels and early visual cortex anatomy using the data from the second GABA measurement where the size of the MRS voxel was proportional to each individual's functional V1 surface size. V1 is known to exhibit a notably higher number of GABA receptors and neurons than adjacent regions (Hendry et al., 1987; Zilles et al., 2002), and hence may possibly contain a higher concentration of GABA; it is thus plausible that within a fixed volume in the medial occipital cortex, the concentration of GABA might be higher for individuals with a larger V1. By scaling the MRS voxel accordingly, we aimed to maintain the proportion of other areas that may also be captured by the GABA volume constant across participants. However, this kind of measurement poses several problems for an inter-subject comparison: the noise levels differ greatly between differently sized voxels, and their positioning may vary between participants (see Materials and Methods). Despite these potential problems, the GABA levels estimated from the adjusted MRS voxels in our second scan converged well with those estimated from the constant one-sized voxel ($r = .716$, $p < .001$). Likewise, replicating the results from the other MRS measurement, there was a significant positive relationship between GABA (GABA/tNAA) and the surface size of central V1 ($r = .453$, $p = .045$, see Fig. 4). None of the other relationships with early visual cortex anatomy reached significance in this measurement (see Fig. 4 and Table 1, fourth row).

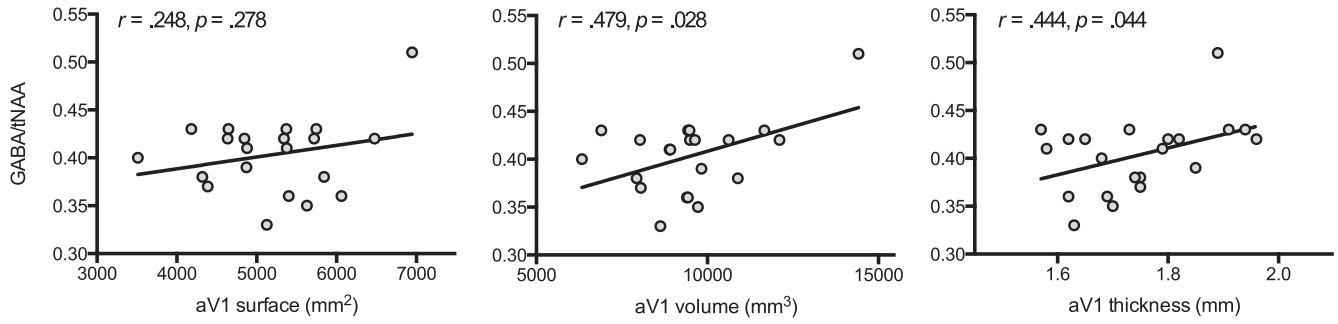

Fig. 3. Overall aV1 size and its relationship to GABA levels in the medial occipital cortex. The figure conventions used are identical to those in Fig. 2. The GABA level was significantly related to anatomically mapped overall aV1 volume and thickness, but not to surface size. Individuals with a bigger aV1 tended to have a higher concentration of GABA in this region.

Table 2
Statistical relationships between the concentration of Glx or GABA/Glx ratios in medial occipital cortex and measures of early visual cortex anatomy.

	Glx (glutamate and glutamine)		GABA/Glx ratio	
	Equally sized MRS voxel (Glx/tNAA)	Proportional MRS voxel ($N = 20$) (Glx/tNAA)	Equally sized MRS voxel	Proportional MRS voxel
V1 volume	−.013 (.956)	.227 (.336)	.354 (.116)	.166 (.483)
V1 surface size	.075 (.747)	.209 (.375)	.326 (.149)	.182 (.443)
V1 cortical thickness	−.158 (.494)	−.125 (.599)	.135 (.561)	.151 (.526)
V2 volume	.261 (.253)	.026 (.912)	−.030 (.897)	.094 (.695)
V2 surface size	.113 (.625)	−.062 (.795)	−.050 (.831)	.008 (.974)
V2 cortical thickness	.381 (.089)	.179 (.451)	−.074 (.751)	.190 (.423)
V3 volume	.337 (.136)	−.128 (.592)	.048 (.835)	.217 (.359)
V3 surface size	.101 (.663)	−.335 (.149)	.047 (.841)	.223 (.345)
V3 cortical thickness	**.452 (.040)**	.327 (.159)	−.049 (.833)	.014 (.953)
aV1 volume	−.062 (.791)	−.264 (.261)	**.487 (.025)**	**.487 (.029)**
aV1 surface size	−.184 (.424)	−.201 (.396)	.380 (.089)	.271 (.247)
aV1 cortical thickness	.179 (.438)	−.275 (.240)	.256 (.263)	**.581 (.007)**

Note: The values indicate bivariate correlations, the *p*-values in brackets their respective significance levels. Significant correlations ($p < .05$) are written in bold. Abbreviations: aV1 = anatomically estimated (i.e. overall) V1 (Hinds et al., 2008).

In contrast to GABA, again there was no significant relationship between Glx and V1 surface size, nor with any of the other early visual cortex anatomy measures (see Table 2, second row).

Our prior hypothesis addressed the relationship between the concentration of inhibitory GABA and V1 anatomy. However, it could also be the case that the relevant factor is, in fact, the balance between inhibition and excitation rather than the level of cortical inhibition alone. To investigate this question, we also assessed the relationship between V1 anatomy and the ratio of GABA and Glx. Similarly to the correlation between GABA concentration and aV1 volume, we found significant positive correlations between the GABA/Glx ratio and aV1 volume in both MRS measurements (see Table 2, third and fourth row). In contrast, the correlation between the GABA/Glx ratio and V1 surface area was non-significant. None of the differences between the correlations between GABA alone and V1 anatomy and the correlations between GABA/Glx and V1 anatomy were statistically significant (all $p > .05$). Taken together, there is no indication that the balance between GABA and Glx is a better predictor of V1 anatomy than the concentration of GABA alone.

As we found a significant relationship between GABA and overall aV1 volume, we also ran a surface-based morphometric volume analysis of the whole brain as an additional control. We used Qdec implemented in FreeSurfer to detect cortical clusters anywhere in the brain that might show significant relationships between volume and the measured GABA levels (GABA/tNAA; see Methods). Significant clusters were found in the medial occipital lobe, with the cluster in the right hemisphere surviving the multiple comparison correction (see Fig. 5 and **Supplementary Table S1**).

Discussion

The results of previous studies, linking V1 surface size to Gamma peak frequency (Schwarzkopf et al., 2012), and Gamma peak frequency to GABA levels (Edden et al., 2009; Muthukumaraswamy et al., 2009), have hinted at a potential relationship between V1 surface size and local GABA levels. To the best of our knowledge however, no study has looked at this link directly. Our findings present the first evidence for a positive relationship between V1 size and GABA concentration. Individuals with larger V1 surface areas tended to have higher levels of GABA, while there was no such relationship for Glx or the ratio of GABA and Glx. The association with GABA was present for central V1 surface size across two different and separate MRS measurements. For overall aV1 volume, we also found a significant positive relationship with GABA and the ratio of GABA and Glx. Furthermore, a whole brain volume analysis confirmed the specificity of the relationship with GABA, as only a cluster in the medial occipital cortex survived the multiple comparison correction.

Interestingly, a recent study failed to replicate the significant relationship previously reported between GABA concentration and gamma peak frequency (Cousijn et al., 2014). In light of our findings, it is possible that the observed relationship between GABA and gamma peak frequency is due to the variance that both share with V1 surface size, and hence the lack of a *direct* relationship might cause potential discrepancies between different studies. However, it is also possible that methodology might have played a role. Cousijn et al. (2014) used an MRS method that relies on the accurate post-processing of unedited short-TE spectra. This technique requires ideal conditions for data acquisition (Near et al., 2013). In contrast, the two studies which did find a link between gamma peak frequency and GABA levels (Edden et al., 2009; Muthukumaraswamy et al., 2009) applied J-difference editing using MEGA-PRESS for their MRS measurements, which may be considered the gold-standard for in vivo brain GABA measurements (Mullins et al., 2014).

GABA levels in the occipital lobe of males are highly stable over long periods of time (Near et al., 2014). It is believed that the GABA signal detectable by MRS arises mostly from the cytoplasmic GABA pool in GABAergic neurons, which may act as a back-up reservoir for the vesicular GABA storage (Maddock and Buonocore, 2012). It has been acknowledged that the GABA signal detectable by MEGA-PRESS is confounded by signals derived from macromolecules, with a consensus on how to tackle the problem still lacking. However, this problem seems to be more severe in studies with clinical populations, while studies on the role of GABA for behavioral functions may be less confounded (Mullins et al., 2014).

What are the physiological underpinnings that explain the relationship between V1 surface size and the concentration of GABA? Interestingly, a cross species investigation found that layer IV of V1, which is one of the cortical layers with the highest density of $GABA_A$ receptors (Zilles et al., 2002), is much thicker in larger brains (with larger V1), even when the overall V1 cortical thickness remains the same (Rockel et al., 1980). If this also applies to individual differences in humans, which is currently unknown, then an increase in V1 surface size would be related to a thicker layer IV—which would result in an over proportional number of $GABA_A$ receptors in an individual with a larger V1. Furthermore, if the number of $GABA_A$ receptors, in turn, translates to the concentration of MRS assessed GABA, then a higher GABA concentration could be indicative of a larger V1 surface area.

The idea that GABA concentration and V1 surface size might be interrelated has been suggested by previous findings. Schwarzkopf et al. (2012) hypothesized that local field homogeneity might be increased in a larger V1. That is, in a larger V1, the ratio of neurons that lie in regions where all neurons show relatively homogenous orientation preferences versus neurons that lie in regions where neurons show a larger variety of orientation preferences might be higher. It is known

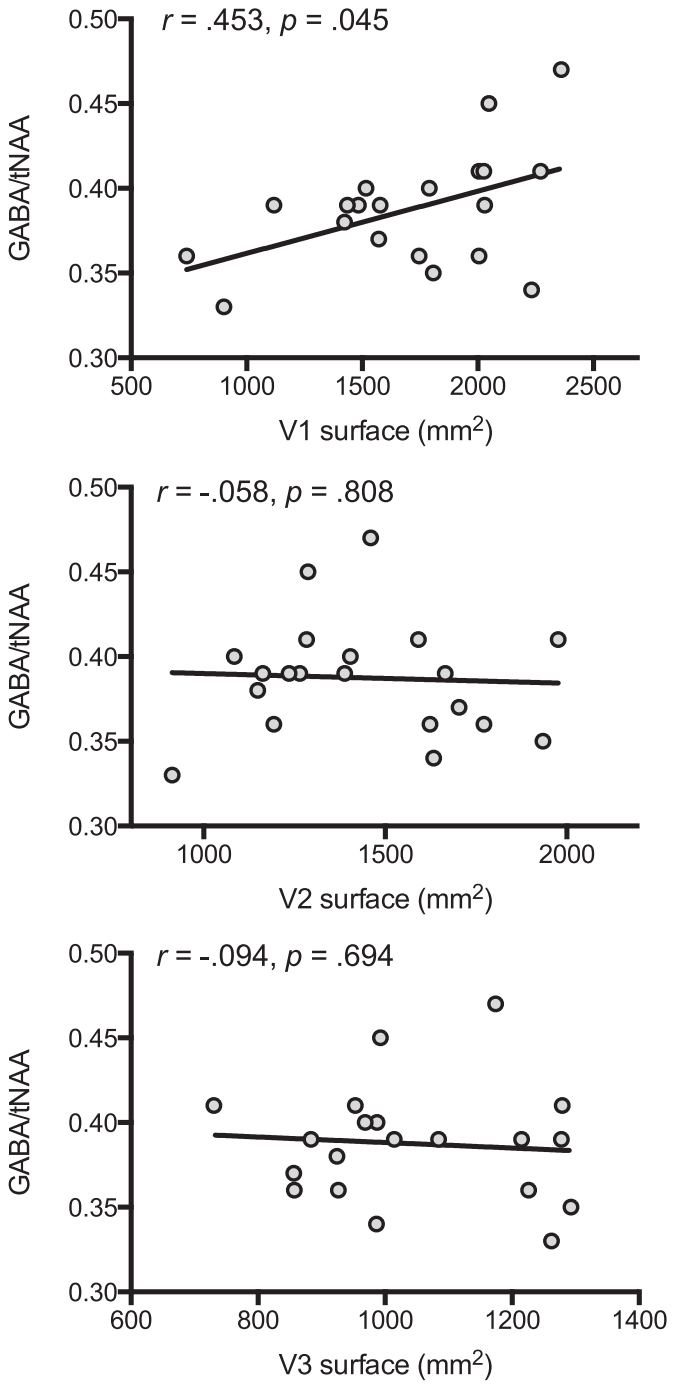

Fig. 4. Results with a proportionally-sized MRS voxel. The same figure conventions as in Fig. 2 are used. As with the MRS voxel of a fixed size, individual GABA concentration in medial occipital cortex was significantly predicted by the functionally defined V1 surface size: individuals with a larger V1 tended to have higher levels of the inhibitory neurotransmitter in this region. No significant correlations were found with V2 or V3 surface size.

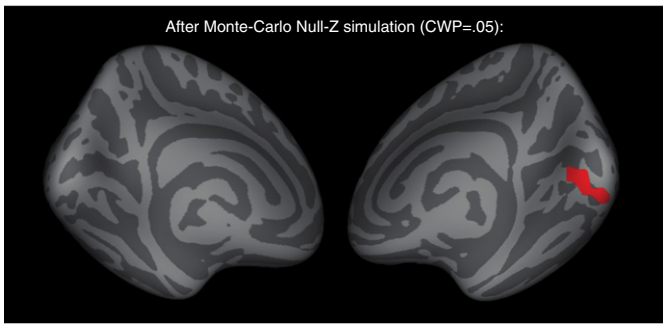

Fig. 5. Exploratory whole brain volume analysis with FreeSurfer's Qdec application using GABA concentration as independent variable. Only a volume cluster in the right medial occipital cortex (indicated in red) showed a significant relationship with GABA that survived the multiple comparison correction using Monte Carlo Null-Z simulation at a cluster-wise probability threshold (CWP) of 5%.

that single neurons within such a homogenous environment are more selective for certain orientations than neurons in a more heterogenous environment (Nauhaus et al., 2008). These strongly selective neurons, on the other hand, appear to receive much more inhibition than less orientation-selective neurons (Li et al., 2008), a finding that is further supported by the observation that the administration of a GABA antagonist or the suppression of GABAergic inhibition reduces their orientation-specificity (Tsumoto et al., 1979; Wolf et al., 1986). Taken together, these observations suggest that the proportion of strongly selective, and hence more strongly inhibited neurons might be higher in larger compared to smaller V1, an assumption that would again hint at a link between V1 surface area and the local concentration of GABA that we found in this study.

However, it could also be argued that the observed relationship between GABA and central V1 surface size measured by MRS is due to the fact that V1 contains a larger number of GABAergic neurons and receptors than adjacent areas (Hendry et al., 1987; Zilles et al., 2002). If this translates into a higher concentration of the neurotransmitter itself, then the positive correlation between GABA and V1 surface size could simply be due to the possibility that with a larger V1, an MRS voxel of a fixed size simply captures less of the surrounding areas than with a smaller V1. However, our second measurement using a V1-proportional MRS voxel speaks against this conclusion. The GABA concentrations measured here were strongly convergent with those of the first measurement, and they again correlated significantly positively with central V1 surface size.

Apart from functionally defined V1 surface size, we also found a significant relationship between GABA and anatomically mapped overall aV1 volume that could not be explained by the mere gray matter proportion in the MRS voxel. Hence, not only individuals with a larger V1 surface area, but also with a larger aV1 volume had a higher concentration of GABA; however, this relationship was less consistent across the two GABA measurements than the relationship with the functionally defined V1 surface area. V1 is special among the brain areas in that differences in its thickness across different species, which contributes to cortical volume, are not only due to differences in the amount of neuropil, but also due to differences in the number of neurons (Carlo and Stevens, 2013; Rockel et al., 1980). In addition, as mentioned previously, V1 is known to contain a much higher proportion of GABAergic neurons and receptors than adjacent areas (Hendry et al., 1987; Zilles et al., 2002). If this translates into GABA concentration, a positive relationship between V1 volume and GABA levels is plausible.

It is worth noting that previously observed relationships between behavior and surface area have been restricted to central V1 (Bergmann et al., 2014, 2015; Genç et al., 2013; Schwarzkopf and Rees, 2013; Schwarzkopf et al., 2011; Song et al., 2013). Likewise, in this study, GABA levels only correlated with the surface area of functionally defined central V1 and not anatomically mapped overall aV1. In our sample, there was only a moderate correlation between overall aV1 and central V1 surface size ($r = .519, p = .018$), indicating that only $.519^2 = 27\%$ of the variance is shared while the rest seems to be influenced by other, non-central factors. This underlines the unique and specific relationship between central V1 surface area and behavior, and might hint at partly independent genetic factors that influence the size of overall aV1 surface size and central cortical magnification.

Taken together, our results illustrate the importance of the macroanatomical layout of V1 for individual neural function. Future research is needed to investigate whether this link might—at least in

part—offer a physiological explanation of the previously observed associations between V1 surface area and perception or cognition.

Author Contributions

J.B. and J.P. conceived the study, all authors designed the experiments, J.B. and U.P. conducted the MRS measurements and analyzed the results, J.B. and E.G. conducted the fMRI retinotopic measurements and analyses, J.B. and J.P. wrote the manuscript and all authors edited the manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.neuroimage.2015.09.036.

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