GABA levels in ventral visual cortex decline with age and are associated with neural distinctiveness

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Abstract

Age-related neural dedifferentiation – reduced distinctiveness of neural representations in the aging brain– has been associated with age-related declines in cognitive abilities. But why does neural distinctiveness decline with age? Based on prior work in non-human primates, we hypothesized that the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) declines with age and is associated with neural dedifferentiation. To test this hypothesis, we used magnetic resonance spectroscopy (MRS) to measure GABA and functional MRI (fMRI) to measure neural distinctiveness in the ventral visual cortex in a set of older and younger participants. Relative to younger adults, older adults exhibited lower GABA levels and less distinct activation patterns for faces and houses in the ventral visual cortex. Furthermore, individual differences in GABA within older adults predicted individual differences in neural distinctiveness even after controlling for gray matter volume and age. These results provide novel support for the view that age-related reductions of GABA contribute to age-related reductions in neural distinctiveness (i.e., neural dedifferentiation) in the human ventral visual cortex.

Keywords: *aging, dedifferentiation, fMRI, GABA, multivariate pattern analysis, spectroscopy*

Significance Statement

Neural representations in the ventral visual cortex are less distinguishable in older compared to younger humans, and this neural dedifferentiation is associated with age-related cognitive deficits. Animal models suggest that reductions in the inhibitory neurotransmitter gamma aminobutyric acid (GABA) may play a role. To investigate this hypothesis, we combined functional magnetic resonance imaging (fMRI) and magnetic resonance spectroscopy (MRS) in a study of the human ventral visual cortex. We observed reduced distinctiveness of neural patterns and reduced GABA levels in older compared to younger adults. Furthermore, older adults with higher GABA levels tended to have more distinctive neural representations. These findings suggest that reduced GABA levels contribute to age-related declines in neural distinctiveness in the human ventral visual cortex.

Introduction

Fluid processing abilities (cognitive abilities that do not depend on how much you know) often decline with age, even in the absence of disease (Park et al., 2002). Age-related reductions in neural distinctiveness (the extent to which different stimuli activate distinct neural representations) have been hypothesized to play a role in such declines (see Koen & Rugg, 2019 for a recent review). For example, the neural activation patterns associated with different categories of visual stimuli (e.g., faces and houses) are more similar in old compared to young adults (Park et al., 2004; Carp et al., 2011) and individual differences in neural distinctiveness account for as much as 30% of the variance in fluid processing performance among older adults (Park et al. 2010). Furthermore, computational models have demonstrated that declines in neural distinctiveness could potentially account for a number of age-related behavioral impairments (Li & Lindenberger, 1999; Li, Lindenberger, & Sikström, 2001; Li & Sikström, 2002). Conversely, neural distinctiveness is not associated with crystallized intelligence (cognitive processing that depends critically on knowledge), and crystallized intelligence typically does not decline with age.

An important open question is why does neural distinctiveness decline with age? One hypothesis is that age-related reductions in the brain's major inhibitory neurotransmitter, gamma aminobutyric acid (GABA), plays a role (Hua et al., 2008). GABA is critical for resolving cortical competition between different representations (Isaacson & Scanziani, 2011), so a reduction in GABA might plausibly lead to less distinct activation patterns for competing stimuli. Furthermore, GABA concentrations in visual cortex are reduced in older compared to younger adults (Simmonite et al., in press) and individual differences in GABA concentrations in

pre-supplementary motor area and occipital cortex predict individual differences in cognitive performance in older adults (Hermans et al., 2018; Simmonite et al., in press).

Findings from non-human primates further support this hypothesis. Leventhal et al. (2003) found that visual neurons in young monkeys responded more selectively to stimuli with specific orientations and directions than visual neurons in old monkeys. However, electrophoretic application of GABA, or the $GABA_A$ receptor agonist muscimol, to the neurons in older monkeys made these cells respond selectively, like the neurons in young monkeys. Conversely, application of the $GABA_A$ receptor antagonist bicuculline to visual neurons in young monkeys made them respond less selectively, like the neurons in old monkeys. Together, these results demonstrate that changes in GABA activity can cause changes in neural selectivity at the level of individual receptive fields in non-human primates. Whether age-related reductions of GABA activity play a role in age-related reductions of neural distinctiveness in humans remains unexplored.

Inspired by these prior findings, we tested this hypothesis. Specifically, we combined magnetic resonance spectroscopy (MRS) with functional MRI (fMRI) to measure both GABA levels and neural distinctiveness in the ventral visual cortex of young and old adults. We hypothesized that both measures would be reduced in the older group compared with the younger group. We also hypothesized that individual differences in GABA would be associated with individual differences in neural distinctiveness within the older adults.

Materials and Methods

Ethics Statement. The University of Michigan Institutional Review Board approved the study procedures. All participants provided verbal and written consent prior to the study.

Participants. 37 younger adults (mean age = 23.02 years, SD = 3.01, range = 18-29, female = 20) and 51 older adults (mean age = 70.47 years, SD = 4.75, range = 65-87, female = 31) from the local Ann Arbor community participated in the experiment as part of the Michigan Neural Distinctiveness (MiND) project (Gagnon et al., 2019). All participants were native English speakers, right handed, physically and psychologically healthy, not taking vascular or psychotropic medication, had normal or corrected-to-normal vision, and had no other MRI contraindications. Finally, all participants scored greater than 26 on the Montreal Cognitive Assessment (MoCA; Nasreddine et al., 2005). See Gagnon et al. (2019) for more details regarding the MiND project design.

Experimental design. Prior to fMRI scanning, participants completed a brief visual acuity test derived from the NIH Toolbox for Assessment of Neurological and Behavioral Function (Gershon et al., 2010). Briefly, participants viewed letters sequentially presented on an iPad at a distance of three meters. Participants verbally stated what letters they saw on the screen, and the letters became smaller after each correct response. The NIH Toolbox software calculates a LogMAR score (modified Snellen visual acuity score) and then converts it to a standard score of visual acuity. During fMRI scanning, participants completed a visual face/house task similar to that used by Park et al. (2010). The task consisted of one six-minute fMRI run with six 20-second blocks of faces and six 20-second blocks of houses, in pseudorandom order. A 10-second

fixation block preceded and followed each experimental block. During the face blocks, participants viewed greyscale images of male faces. During the house blocks, participants viewed greyscale images of houses. Each stimulus appeared for 500 milliseconds, after which there was a 500 millisecond interstimulus interval (ISI). We instructed participants to press a button with their right index finger whenever they saw a female face during the face blocks, and whenever they saw an apartment building during the house blocks. Such target images occurred approximately once per minute. We presented the stimuli using E-Prime 2.0 on a back-projection system. We recorded participants' responses using a Lumina response pad (Cedrus).

fMRI data acquisition. We collected fMRI data with a 3T GE MRI scanner at the University of Michigan's Functional Magnetic Resonance Imaging Laboratory. We acquired blood oxygen level dependent (BOLD) images using a single-shot gradient echo (GRE) reverse spiral pulse sequence (TR = 2000ms, TE = 30ms, FOV = 220mm, voxel size = 3.4375 x 3.4375 x 3mm, 43 axial slices). We collected high-resolution T1 images using an SPGR (3D BRAVO) sequence with the following parameters: Inversion Time (TI) = 500 ms; flip angle = 15°; Field of View (FOV) = 256 x 256 mm; 1 x 1 x 1 mm voxels; 156 axial slices.

Magnetic resonance spectroscopy data acquisition. We collected MRS data using the same scanner, during a different scanning session. We placed 3x3x3cm voxels in the ventral visual cortex near the left and right mid-fusiform gyrus. Specifically, we customized voxel placement for each participant to maximize overlap with ventral visual fMRI activity during the face/house task from the previous fMRI session (using a contrast of Face and House vs Fixation). We also collected MRS data from voxels placed in the auditory cortex and sensorimotor cortex (Gagnon

et al., 2019). We acquired GABA-edited MR spectra using a MEGA-PRESS sequence using the following acquisition parameters: TE = 68 ms (TE1 = 15ms, TE2 = 53 ms); TR = 1.8s; frequency selective editing pulses (14 ms) applied at 1.9 ppm (ON) and 7.46 ppm (OFF); total scan time, approximately 8.5 min per voxel.

The MEGA-PRESS sequence collects one MR spectrum while editing pulses are applied at 1.9 parts per million (ppm) and another MR spectrum while these editing pulses are not applied. The GABA signal at 3 ppm is affected by these editing pulses (i.e., it is coupled), while non-GABA signals near 3 ppm (e.g., Creatine) are not affected. Subtracting the two spectra leaves a measurable GABA signal.

Statistical analysis.

fMRI Pre-processing. We k-space despiked, reconstructed, and corrected the MRI data for heart beat and respiration using the RETROICOR algorithm (Brooks et al., 2008). We then slice time corrected the data using the spm_slice_timing function from SPM (https://www.fil.ion.ucl.ac.uk/spm) and motion corrected using mcflirt from FSL 5.0.7 (www.fmrib.ox.ac.uk/fsl). We resampled the data into two-dimensional cortical surfaces (one for the left hemisphere and one for the right hemisphere) based on a white/gray matter segmentation of each subject's own high-resolution structural image computed using Freesurfer's recon-all function (version 6, https://surfer.nmr.mgh.harvard.edu/). We spatially smoothed the data within each cortical surface using a 5-mm two-dimensional smoothing kernel. We used Freesurfer's FSFAST processing stream to fit a general linear model to the fMRI time series at each point, or

vertex, on the cortical surface. The model included box-car regressors corresponding to the face and house conditions. We convolved each regressor with a standard hemodynamic response function.

We created participant-specific structural masks of the bilateral fusiform gyrus and bilateral parahippocampal gyrus using the cortical parcellation of each participant's brain generated by Freesurfer's recon-all function (which also generated gray matter volume estimates of the aforementioned gyri). We then computed participant-specific functional regions-of-interest (ROIs) within these structural masks based on activation (i.e., beta values) during the face and house conditions. Specifically, we sorted the beta values for each condition at all the vertices within the structural mask from largest to smallest. We added the most activated vertex from both the face and house conditions to the ROI, followed by the second most activated vertex in each condition, and then the third most active, and the fourth, and so on. If the next most active vertex in one of the conditions was already included in the ROI (based on the other condition), then we added the next most active vertex from that condition that was not already in the ROI. We used this process to create functional ROIs of varying size (from 1000 vertices up to the size of the entire structural mask) to test whether any observed age-related differences in neural distinctiveness depended on the number of vertices selected. See Figure 1 for a participant-specific example with a functional ROI of 5,000 vertices. In the end, this process produced functional ROIs that only included the most activated vertices, and that included an equal number of face-active and house-active vertices. This allowed us to compute the neural distinctiveness of the two activation patterns in an unbiased manner.

Following Haxby et al. (2000) and previous work by Park et al. (2011), we computed the distinctiveness of face and house activations patterns by subtracting the similarity of activation patterns from different conditions (i.e., faces versus houses) from the similarity of activation patterns within the same condition (i.e., faces versus faces and houses versus hours). If face and house activation patterns are highly distinct, then within-condition similarity should be greater than between-condition similarity. On the other hand, if face and house patterns are not very distinct, then within- and between-condition similarity should differ to a lesser degree. While the accuracy of a machine learning classifier (e.g. a support vector machine) is often used as a measure of neural distinctiveness (Park et al., 2010; Fandakova et al., 2019), our use of a block design with 12 blocks meant classification accuracy could only take on one of 13 discrete values corresponding to the number of 12 blocks that were correctly classified (e.g 0/12, 1/12, 2/12 etc). Furthermore, classifier accuracy was at ceiling for the majority of participants. We therefore used the correlation-based measure as it is a more fine-grained continuous measure that is not susceptible to ceiling effects.

We computed within- and between-condition similarity by calculating (1) the average (Fisher-transformed) correlation between all pairs of blocks within the same condition (i.e., all the face-face pairs and house-house pairs) and (2) the average (Fisher-transformed) correlation between all pairs of blocks from different conditions (i.e., all the face-house pairs). We defined neural distinctiveness as the difference between these measures of within- and between-condition similarity. As this measure of neural distinctiveness is the difference between two correlations, it can range from -2 to 2, with larger numbers indicating greater distinctiveness and smaller numbers indicating less distinctiveness.

To assess age differences in neural distinctiveness we used pairwise t-tests separately at each functional mask size of 1,000, 2,000, 5,000, and 10,000 vertices. To examine age differences in neural distinctiveness in the context of gray matter volume and visual acuity, we first conducted planned one-tailed, two-sample, t-tests of lateral fusiform and parahippocampal gyri gray matter volume as well as visual acuity. We then used a multiple linear regression model with age group (younger, older) and a composite of gray matter volume as predictor variables and neural distinctiveness (within a functional mask size of 5,000 vertices; see *Neural distinctiveness* for rationale on using 5,000 vertices) as the outcome variable, followed by a separate model using visual acuity as a predictor variable in place of gray matter volume. We also examined potential age differences in the individual components (within- and between- condition similarity) of our neural distinctiveness measure to follow work done previously by Carp et al. (2011). As we had no *a prior* hypotheses regarding the directionality of age differences in these measures we conducted two-tailed, two sample, t tests on within-condition similarity and between-condition similarity. All statistical analyses of neural distinctiveness were conducted using *R* software (R Core Team, 2017).

Magnetic resonance spectroscopy analysis. We used Gannet 3.0 (Edden et al., 2013) to analyze the MR spectra and estimate GABA levels in each voxel. Gannet performs time domain frequency and phase correction of the MR spectra using spectral correction, fits a Gaussian to the GABA signal in the GABA-edited spectrum, and computes the area under the Gaussian. It also fits a mixed Gaussian-Lorentzian model to the water signal and estimates GABA concentration as the GABA/water ratio.

Gannet also coregisters each MRS voxel to the T1-weighted SPGR image and calls SPM to segment the T1-weighted image. It then uses the results to estimate the fraction of gray matter, white matter, and cerebrospinal fluid within the MRS voxel and computes an estimate of GABA concentration that is corrected for the tissue composition.

Finally, we note that the GABA peak in the GABA-edited spectrum is contaminated by coedited macromolecules. In keeping with previous reports (Edden et al., 2014), we will refer to our measurements using the term GABA+ (i.e., GABA + macromolecules) to reflect this limitation.

We used planned one-tailed, two-sample, t tests to examine age differences in raw GABA+ concentrations. To test potential hemisphere contributions to age differences in raw GABA+ estimates we used a 2 (age group: younger, older) x 2 (hemisphere: left, right) mixed design ANOVA (age group as a between-subjects factor and hemisphere of voxel placement as a within-subjects factor) for raw GABA+. To examine individual differences in neural distinctiveness and raw GABA+ within older adults we conducted simple linear regression using raw GABA+ as our predictor variable and neural distinctiveness as our outcome variable. We then conducted multiple linear regression including gray matter volume and age (as a continuous variable) as additional predictor variables. To assess whether the relationship between neural distinctiveness and GABA+ was specific to the visual cortex, we used separate simple linear regression models using raw sensorimotor cortex and auditory cortex GABA+ estimates as predictor variables and ventral visual neural distinctiveness as the outcome variable. To assess whether local tissue composition explained any observed relationships with GABA+, we

repeated the above statistical tests using tissue-corrected GABA+ estimates instead of raw GABA+. All statistical analyses of GABA+ were conducted using *R* software (R Core Team, 2017).

Results

GABA+ concentrations. First, we assessed potential age differences in GABA+ concentrations in the ventral visual cortex. Consistent with prior work (Simmonite et al., in press), average raw GABA concentrations were significantly lower in the old than in the young adults ($t(85.52) = 4.83$, $p < 0.001$, one-tailed t test; **Fig 2**). The raw measurements in the left and right hemisphere voxels were significantly correlated ($r(84) = .49$, $p < .001$) and a mixed design ANOVA (age group as a between-subjects factor and hemisphere of voxel placement as a within-subjects factor) found no significant interaction between hemisphere and age ($F(1,84) = .25$, $p = .62$).

Age still had a significant effect on tissue-corrected GABA+ estimates ($t(84.59) = 4.67$, $p < .001$, one-tailed t test), suggesting that structural differences in local tissue composition cannot completely explain age differences in ventral visual GABA+ concentrations. Left and right GABA+ hemisphere measures were still significantly correlated after using tissue-corrected GABA+ rather than raw GABA+ estimates ($r(84) = .46$, $p < .001$), and we again failed to find a significant hemisphere by age interaction using tissue-corrected GABA+ ($F(1,84) = .29$, $p = .592$). We therefore averaged the GABA+ measures from the two hemispheres for subsequent regression analyses (*see Neural Distinctiveness and GABA+ concentrations*).

Neural distinctiveness. Next, we investigated the relationship between age and neural distinctiveness in the ventral visual cortex. Figure 3 plots the average neural distinctiveness in young and old adults as a function of ROI mask size. Using pairwise t tests for each functional mask size we found that neural distinctiveness was lower in older adults compared to younger adults across all mask sizes (all p's < .01). This result replicates previous findings of age-related neural dedifferentiation in the human ventral visual cortex (Park et al., 2004; Payer et al., 2006; Park et al., 2010). As no interaction was observable between ROI mask size and age group, we chose an intermediate ROI size of 5,000 vertices for all subsequent statistical analyses using neural distinctiveness.

Previous work suggests that age-related declines in regional gray matter volume may contribute to differences in neural distinctiveness (Park et al., 2012) and gray matter volume was lower in the old adults than in the young adults in the fusiform gyrus (left fusiform $t(70.17) = 4.71$, $p < 0.001$; right fusiform $t(57.76) = 6.16$, $p < 0.001$) and parahippocampal gyrus (left parahippocampal $t(52.82) = 4.65$, $p < 0.001$; right parahippocampal gyrus ($t(69.56) = 5.63$, $p < 0.001$, one-tailed t test). Nevertheless, neural distinctiveness was lower in old adults than in young adults even after controlling for gray matter volume ($\beta(85) = 0.14$, $p = 0.025$). This finding supports the notion that age-related structural changes within the visual cortex cannot completely explain age-related neural dedifferentiation.

It is also possible that age-related declines in peripheral visual ability (Greene & Madden, 1987) contribute to neural dedifferentiation in the visual cortex. However, the older adults in our study (who were allowed to use eyeglasses and/or contacts) did not have significantly reduced visual

acuity relative to the younger adults (t(58.81.26) = 0.41, p = 0.34, one-tailed t test), and neural distinctiveness remained lower in the old than in the young adults after controlling for visual acuity (β(84) = 0.14, p = 0.004).

In a previous study, we found evidence for both an age-related increase in between-condition similarity and an age-related decrease in within-condition similarity (Carp et al., 2011). In the present study, however, we only found evidence of an age-related decrease in within-condition similarity (t(80.64) = -3.90, p < .0001, two-tailed t test) without a significant age-related change in between-condition similarity (t(70.72) = - 0.38, p = .704, two-tailed t test). This suggests that the observed age-related reductions in neural distinctiveness may be due primarily to reductions in reliability (i.e., noisier, or less consistent, neural activation patterns) rather than increased representational similarity for different categories per se.

Neural distinctiveness and GABA+ concentrations. We also examined the relationship between individual differences in GABA+ and individual differences in neural distinctiveness within older adults through multiple linear regression. Old adults with higher levels of raw GABA+ exhibited increased neural distinctiveness (β(49) = .27, p = 0.038; **Fig 4**), even after controlling for individual differences in gray matter volume and age (β(47) = .31, p = 0.024). GABA+ was also still significantly associated with distinctiveness when using tissue-corrected GABA+ estimates rather than raw GABA+ concentrations (β(49) = .28, p = 0.032), and this relationship was still present after controlling for age and gray matter volume within the older adults (β(47) = .30, p = 0.021)

The relationship observed between neural distinctiveness and GABA+ within older adults was specific to the visual cortex. Neither average sensorimotor cortex GABA+ concentrations ($\beta(49) = -0.06$, $p = 0.701$) nor auditory cortex GABA+ concentrations ($\beta(49) = -0.19$, $p = 0.16$) significantly predicted neural distinctiveness within the visual cortex of older adults. Tissue-corrected GABA+ concentrations in sensorimotor cortex and auditory cortex also failed to predict neural distinctiveness (sensorimotor $\beta(49) = -0.04$, $p = 0.776$; auditory $\beta(49) = -0.17$, $p = 0.162$).

Discussion

In this study, we report three main findings. First, GABA+ levels in ventral visual regions are significantly lower in older adults than in young adults. Second, the activation patterns evoked by faces and houses are significantly less distinct in older adults than in young adults. Third, older adults with higher GABA+ levels in the ventral visual cortex exhibit greater neural distinctiveness than participants with lower GABA+ levels. We discuss each finding in turn.

GABA+ levels decline with age. We found that GABA+ levels in ventral visual cortex were significantly reduced in the older group compared with the younger group. This result extends previous MRS studies that have found age-related declines in GABA+ in frontal and parietal cortex (Gao et al., 2013, Porges et al., 2017, Grachev & Apkarian, 2001). It is also consistent with animal work showing a decline in the number of GABA-immunoreactive neurons in the inferior colliculus (Caspary, Milbrandt, & Helfert, 1995), striate visual cortex (Hua et al., 2008), and hippocampus (Stanley & Shetty, 2004), and with the decline of GABA receptor subunits

within primary visual cortex in later adulthood (Pinto et al., 2010). Our results lend support to the notion that GABAergic functioning is reduced in older adults as the visual cortex ages.

On the other hand, our MRS findings differ from those recently reported by Pitchaimuthu et al. (2017), who found increased GABA concentrations in the visual cortex of old compared to young adults within the banks of the calcarine sulcus. Their MRS voxel placement was significantly more posterior than that used for the voxels in the present study, so one possibility is that GABA concentrations do not change uniformly within the visual cortex in later adulthood. However, we recently collected MRS data from 20 older and 19 young adults in an early visual cortex voxel similar to that used by Pitchaimuthu et al. (2017), and we still found a significant reduction in GABA+ in the older group (Simmonite et al., in press). Thus, further research will be necessary to resolve this discrepancy.

Neural distinctiveness declines with age. In keeping with previous reports of age-related neural dedifferentiation (Park et al., 2004; Park et al., 2010; Carp et al., 2011; Koen et al., 2019), we found that neural distinctiveness in ventral visual cortex was reduced in older adults relative to younger adults. This effect was present even after controlling for visual acuity, suggesting that age-related declines in peripheral sensory capabilities cannot completely explain declines in neural distinctiveness. We also found that age-related declines in neural distinctiveness were still present after controlling for gray matter volume reductions of the fusiform and parahippocampal gyri. This result is consistent with a report from Voss et al. (2008) who found that neural dedifferentiation was not related to local gray matter volume differences in the visual cortex of older adults. Likewise, age-related neural dedifferentiation in motor cortex was reported to

survive corrections for local gray matter volume (Carp et al., 2011). Together, these reports suggest that local gray matter differences cannot completely explain reduced neural distinctiveness.

Neural distinctiveness could be reduced in older compared to younger adults for at least three reasons. The most obvious is that the activation patterns in response to faces and houses are more similar to each other in the older vs. younger participants (i.e., the neural representations for the two categories overlap to a greater degree) (Haxby et al., 2001). If so, then the between-condition similarity measure would increase in older adults and neural distinctiveness (calculated as within-condition similarity minus between-condition similarity) would decrease.

A second possibility is that the neural representations *within* each stimulus category become noisier and less reliable. For example, if the activation evoked by faces is inconsistent from block to block then the within-condition similarity of the face blocks will decline, and so will neural distinctiveness. This could result from reduced representational fidelity of individual stimuli (Zheng et al., 2018), as has been shown within blocks of faces (Goh et al., 2010).

A third possibility is that both of these mechanisms are at work. First, within-condition similarity may be lower in old adults than in young adults. Second, between-condition similarity may be higher in old adults than in young adults. Clearly, the operation of both of these mechanisms would also lead to reduced neural distinctiveness in old adults than in young adults.

When examining the components of our distinctiveness measure individually, we found an age-related reduction in within-condition similarity but no difference in between-condition similarity. Thus, the greatest driver of age-related neural dedifferentiation in the present study was a decrease in the reliability of neural activation patterns. Consistent with this interpretation, age-related changes in within-condition similarity were also larger than age-related changes in between-condition similarity in Carp et al. (2011).

Higher GABA+ levels are associated with greater neural distinctiveness. Finally, we found that individual differences in GABA+ in ventral visual cortex were associated with individual differences in neural distinctiveness in the same region of older adults. Specifically, older adults with higher GABA+ levels tended to exhibit greater neural distinctiveness than those with lower GABA+ levels, even after controlling for gray matter volume and age. This relationship in older adults was also region specific as GABA+ in auditory and sensorimotor cortices did not predict neural distinctiveness within the ventral visual cortex.

Statistically, the relationship between GABA+ and neural distinctiveness that we observed in older adults may be due in part to increased variability in GABA concentrations within the ventral cortex of older adults compared with younger adults. Indeed, older adults in our sample have nearly 60% more variance in GABA+ concentrations than the younger adults. A lack in variability in younger adults could potentially hinder the ability to detect a relationship between GABA+ and distinctiveness in that population (a restriction of range problem).

Limitations. Like most imaging studies, the current study is correlational, and so we cannot conclude that reductions in ventral visual GABA+ levels cause neural dedifferentiation, only that GABA+ is associated with distinctiveness. Future studies could examine causal links between GABA+ and neural distinctiveness by manipulating GABA pharmacologically, like recent work with dopamine (Abdulrahman et al., 2015). Another approach would be to examine longitudinal changes in GABA and neural distinctiveness to understand the coupling in the two measures. Another limitation of the current study (and other spectroscopy studies in humans) is that the size of our spectroscopy voxels was large (3x3x3 cm). Our voxel placement therefore includes cortical tissue irrelevant to neural patterns representing face and house information. Finally, MRS estimates of GABA do not measure GABA activity, but only GABA volume and they do not distinguish between intracellular and extracellular GABA. These limitations should presumably make it harder to observe relationships between GABA and distinctiveness, so the fact that we did find a significant relationship suggests that the relationship may be fairly strong.

Conclusions. In closing, we demonstrated that GABA+ concentrations are reduced with age in ventral visual regions. We also found age-related neural dedifferentiation in older compared to younger adults in the same region. Finally, we demonstrated that individual differences in GABA+ concentrations are associated with individual differences in neural distinctiveness within older adults. These findings collectively are consistent with the hypothesis that age-related declines in GABA play a role in neural dedifferentiation within the ventral visual cortex.

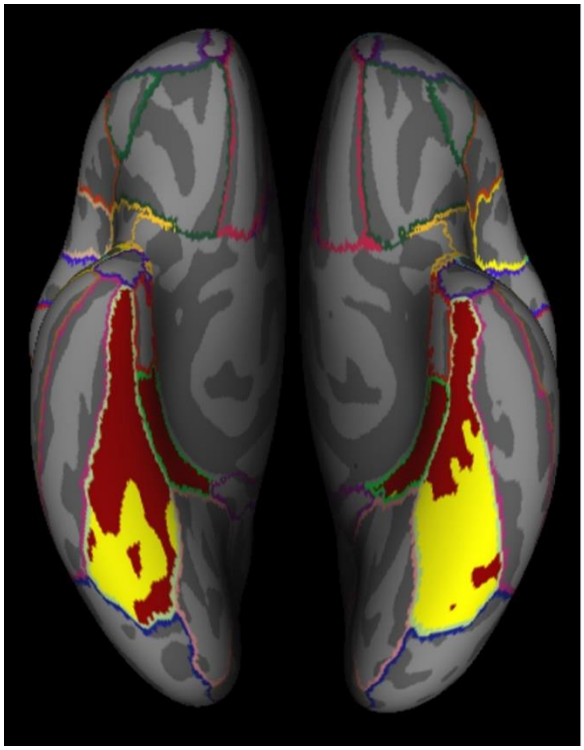

Figure 1. Participant-specific example of ventral visual structural (red) and functional (yellow) ROIs. The functional ROI was created using the 5,000 most activated vertices during the face and house conditions.

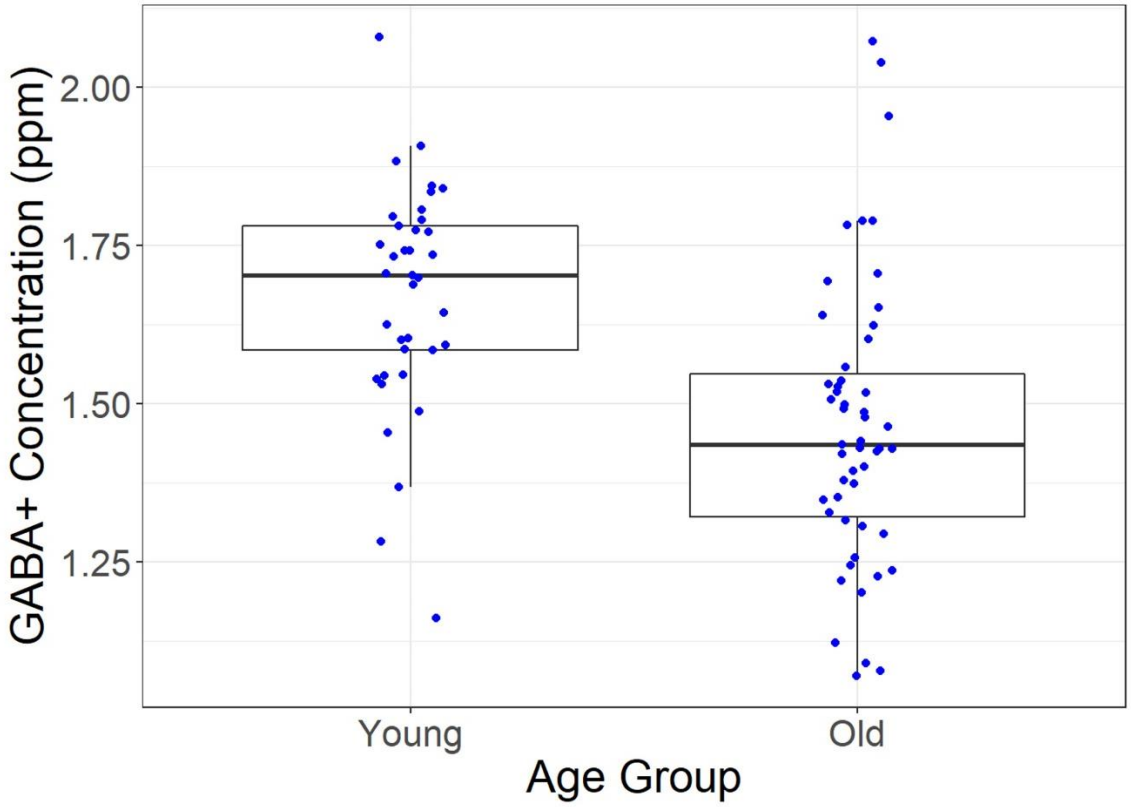

Figure 2. Age-related differences in visual cortex GABA+ levels. GABA+ was significantly reduced in older compared to younger adults.

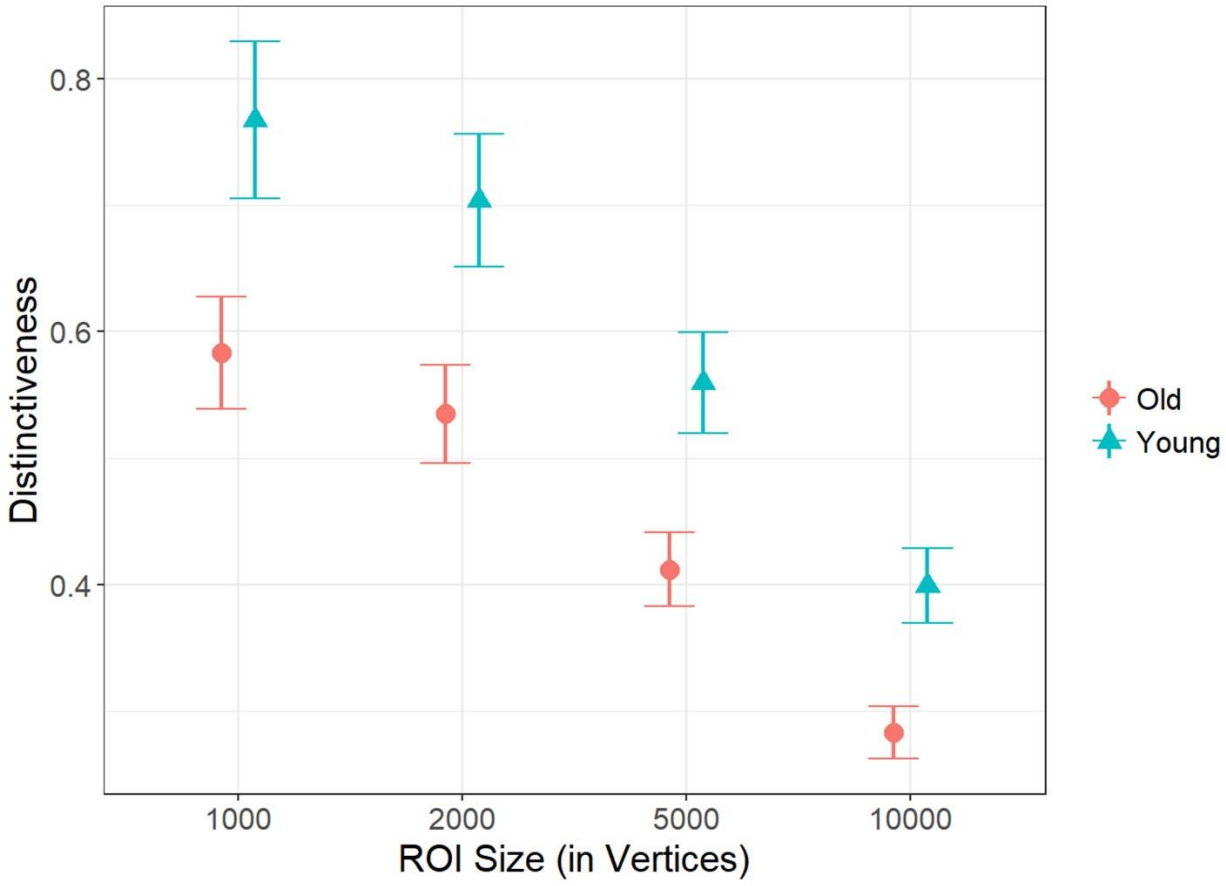

Figure 3. Age-related differences in neural distinctiveness. Neural distinctiveness was significantly reduced within the ventral visual cortex of older (orange circles) compared to younger adults (green triangles) acrosss a range of vertices (1,000-10,000).

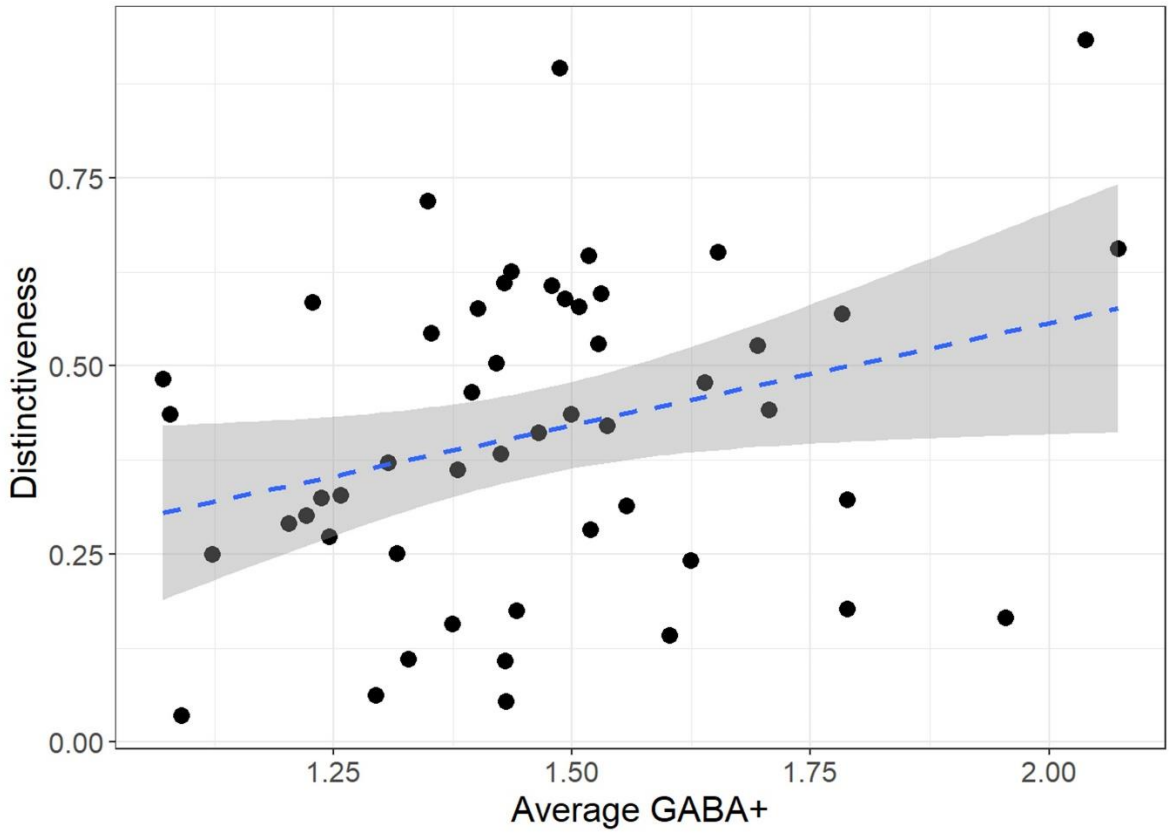

Figure 4. Average GABA+ levels and neural distinctiveness. GABA+ was positively associated with neural distinctiveness in older adults, even after controlling for age and gray matter volume.

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