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Research Report

Dedifferentiation in the visual cortex: An fMRI investigation of individual differences in older adults

Michelle W. Voss[a,b,*], *Kirk I. Erickson*[a,b], *Laura Chaddock*[a,b], *Ruchika S. Prakash*[a,b], *Stanley J. Colcombe*[a,b,1], *Katherine S. Morris*[c], *Shawna Doerksen*[c], *Liang Hu*[c], *Edward McAuley*[c], *Arthur F. Kramer*[a,b]

[a]*Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, USA*
[b]*Department of Psychology, University of Illinois at Urbana-Champaign, USA*
[c]*Department of Kinesiology and Community Health, University of Illinois at Urbana-Champaign, 906 South Goodwin Avenue, Urbana, IL 61801, USA*

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ABSTRACT

Dedifferentiation, or decreased processing specificity, has been suggested to represent a ubiquitous characteristic of cognitive aging. In this study, we examined both age-related differences and intra-group differences in neural specificity in the ventral visual cortex for color, words, faces and places. Our results demonstrated that neural dedifferentiation was not ubiquitous across stimulus categories. Neural dedifferentiation was also relatively stable, across age, in a group of older adults. Older adults with more overall gray matter showed less neural dedifferentiation in the visual cortex. However, regional gray matter volume was not associated with neural dedifferentiation. We illustrate these effects using a discriminability metric, a signal detection theory measure, for neural dedifferentiation that takes into account both magnitude and variance of brain activation. The dedifferentiation measure provides a quantitative means to examine activation patterns and individual difference factors associated with neural dedifferentiation, and to test theories of behavioral dedifferentiation in cognitive aging literature.

1. Introduction

The dedifferentiation hypothesis posits that increasing age is associated with decreased processing specificity, manifested behaviorally by increased covariance in measures of distinct cognitive abilities. For example, it has been shown that with age comes an increase in the correlation among measures of different cognitive constructs such as memory, reasoning, perceptual speed, verbal knowledge, and fluency (Baltes and Lindenberger, 1997; Li et al., 2004), presumably through a decline in fundamental structural or functional neural resources, or both, across the adult lifespan (Lindenberger et al., 2001; Park et al., 2001, 2004; Li et al., 2006). Developmentally, the emergence of neural processing specificity indicates

* *Corresponding author*. Beckman Institute for Advanced Science and Technology, University of Illinois at Urbana-Champaign, 405 N. Mathews Ave, Urbana, IL 61801, USA. Fax: +1 217 333 2922.
E-mail address: mvoss@uiuc.edu (M.W. Voss).
[1] Present address: School of Psychology, Adeilad Brigantia, Penrallt Road, Gwynedd LL57 2AS, U.K. Fax: +44 (0) 1248 38 2599.

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neural differentiation. Therefore, the decreased neural processing specificity that occurs with age is denoted as age-related neural dedifferentiation.

An emergence of brain imaging methods, such as magnetic resonance imaging (MRI) have made it possible to examine behaviorally developed and supported hypotheses of age-related cognitive decline such as dedifferentiation, within the context of structural and functional brain imaging. Structural MRI results demonstrate that while the human brain undergoes widespread gray and white matter tissue atrophy, there is increased regional atrophy in the frontal cortex, caudate nucleus, hippocampus, and cerebellum (Raz et al., 2005). In terms of brain function, age-related neural dedifferentiation has been defined as a change in the spatial pattern of brain activation with age as a result of decreased neural specificity (Park et al., 2001, 2004; Zarahn et al., 2007). Hereafter, the term differentiation is used to denote increased neural specificity, and the term dedifferentiation is used to denote decreased neural specificity. Patterns of brain activation that characterize neural dedifferentiation are more diffuse, in the contralateral brain region, or in a brain region that may or may not be related to task performance in younger adults. Evidence from functional MRI (fMRI) studies suggest that neural dedifferentiation may occur in regions of cortex involved in top-down control (prefrontal), associative binding (hippocampus and parahippocampus), neural object representations (ventral visual cortex), and in primary sensory cortices (Park et al., 2001, 2003; Cabeza et al., 2004; Rajah and D'Esposito, 2005; Payer et al., 2006). Critically, previous research that has studied age-related changes in spatial activation patterns and their relation to cognitive performance and age has used qualitative measures of dedifferentiation (spatial overlap, or presence or absence of spatial activation differences). A quantitative measure of dedifferentiation that takes into account both magnitude and variance of activation would help examine not only age-related differences, but also could potentially be used as a tool to study individual differences within an aging cohort. In the present study, we thus used a quantitative approach to measure neural dedifferentiation in the ventral visual cortex.

The ventral visual cortex provides an excellent landscape to examine age-related differences in neural specificity. Numerous studies have provided evidence for the remarkable and robust capacity of the ventral visual cortex to develop specific regions for processing environmentally familiar stimuli such as faces, the human body, places, objects, words and letter strings, and colors under both passive viewing and task-related conditions (Epstein and Kanwisher, 1998; Kanwisher, 2000; Jobard et al., 2003; Downing et al., 2006). While older adults have demonstrated the capability to retain category specific activation in the ventral visual cortex (Madden et al., 2002; Brodtmann et al., 2003), older adults have also shown more generalized brain activity such that stimulus category-activated voxels overlap to a greater extent in old adults compared with young (Park et al., 2004; Payer et al., 2006). Thus, the study of neural dedifferentiation in the ventral visual cortex provides an opportunity to examine functional brain activation within brain regions shown to have reliable regional specificity in young adults (Epstein and Kanwisher, 1998; Kanwisher, 2000; Gegenfurtner, 2003; Jobard et al., 2003; Downing et al., 2006), and to examine the changes that occur with age (Park et al., 2004; Schmolesky et al., 2000; Godde et al., 2002). Further, as noticed above, a quantitative measure of neural dedifferentiation would facilitate the characterization of individual difference factors that are associated with dedifferentiation in the aging brain.

For example, while it is assumed that dedifferentiation continues to increase throughout the adult lifespan, previous literature has focused only on main effects of age. While indeed strong evidence has been shown to support that older adults are more dedifferentiated than young in the visual cortex (Park et al., 2004), it is also important to examine neural dedifferentiation as a function of age within an old adult sample. This presents an important application of a quantitative measure of neural specificity. It is also possible that normal age-related loss of gray matter volume within the ventral visual cortex, or throughout the brain, plays a role in dedifferentiated visual processing. That is, if neural dedifferentiation is accompanied by structural degeneration in the ventral visual cortex, a strong hypothesis would be that local neuronal integrity moderates the presence (or absence) of neural dedifferentiation. However, if global rather than, or in addition to, local brain volume is associated with dedifferentiation in the ventral visual cortex, this suggests that either other brain structures are important for neural specificity in the visual cortex, or that other functional brain networks are involved. While regional and global structural brain integrity are often cited as potential correlates of dedifferentiation (Park et al., 2001; Cabeza et al., 2004; Rajah and D'Esposito, 2005), neither has been directly examined, and we attempt to do this in the present study.

Overall, there were two primary goals for this study. The first goal was to apply a measure of discriminability, or neural selectivity, to quantitatively measure neural processing specificity (Afraz et al., 2006; Grill-Spector et al., 2007), see Fig. 2. The measure provided a means to examine whether old adults show dedifferentiation in the form of less neural specificity for stimuli localized in the ventral visual system. To assess whether old adults were activating more diffusely as a group compared with young adults, we compared the spatial variability of maximum response for young and old. The second primary goal of this study was to characterize the nature of neural dedifferentiation as an individual difference variable; we examined neural dedifferentiation as a function of age and regional and global brain volume. Specifically, the present study focused on measuring neural dedifferentiation in ventral visual cortex.

2. Results

2.1. *Localization of brain regions for color, word, face and place processing*

2.1.1. *Color*

The maximum *Z* statistic within localized color selective clusters for groups of young and old participants were within 6-mm of each other (within the spatial smoothing kernel of 6-mm FWHM). Therefore, a 1000-mm^3 common group ROI (125 voxels) for young and old was centered on the average coordinates (MNI: −30, −82, −19) of these peaks, from which

young and old activation patterns were compared (see Fig. 1). We also found that subject-specific peaks were not more spatially distributed for old adults compared to young in the color condition ($t(76) = .51$; $p > .05$), see Fig. 1. Therefore, an examination of neural specificity in the color group ROI should not bias our results towards finding more neural specificity for young adults.

2.1.2. *Words*

For the word condition, no common group ROI for young and old was found. When subject-specific peaks were examined for spatial variability, the average x, y and z coordinates for subject-specific word peaks for young and old were within 6-mm of each other and approximately 15-mm superior and anterior to the commonly cited visual word form area (VWFA: MNI −43,−54, −18). Therefore, the average coordinates of the word peaks for young and old (MNI: −40, −44, −6) were used as a reference point from which subject-specific distances were computed for the word condition. Results showed that older adults' word peaks were more spatially dispersed than young adults ($t(76) = 3.48$; $p < .05$) (see Fig. 1). Therefore, the use of the average word peak as a common group ROI for young and old might introduce bias towards finding enhanced neural specificity for young. For this reason, subject-specific peak word ROIs were used to compare neural specificity between young and old.

2.1.3. *Faces and places*

Similar to color processing, the maximum Z statistic for face processing for young and old participants was within 6-mm of each other. A 1000-mm^3 common group ROI (125 voxels) for young and old was centered on these peaks (MNI: 50, −72, −3), from which young and old activation patterns were compared (see Fig. 1). In addition, subject-specific peaks were not more spatially distributed for old adults compared to young in the face condition ($t(76) = 1.47$; $p > .05$), see Fig. 1. Therefore, an examination of neural specificity in the face group ROI should not bias our results towards finding more neural specificity for young adults.

$$\textit{Differentiation Index} = \frac{\mu_{\text{pref}} - \mu_{\text{non-pref}}}{\sqrt{\left(\frac{\sigma^2_{\text{pref}} + \sigma^2_{\text{non-pref}}}{7}\right)}}$$

Fig. 2 – The differentiation index. The differentiation index, a measure of discriminability, measures the specificity of neural response by calculating the separation of the mean responses (μ), scaled by the spread of the mean distributions (where σ represents the standard deviation of response amplitude). The index was computed for the preferred ROI across all stimulus conditions, including the preferred and all non-preferred conditions. Percent signal change was measured relative to the baseline condition for each stimulus condition. For example, the differentiation index for specificity of response to faces was computed as the percent signal change in the FFA ROI minus the average percent signal change within FFA during the other six localizer conditions, divided by the average standard deviation of percent signal change to all seven localizer conditions within FFA.

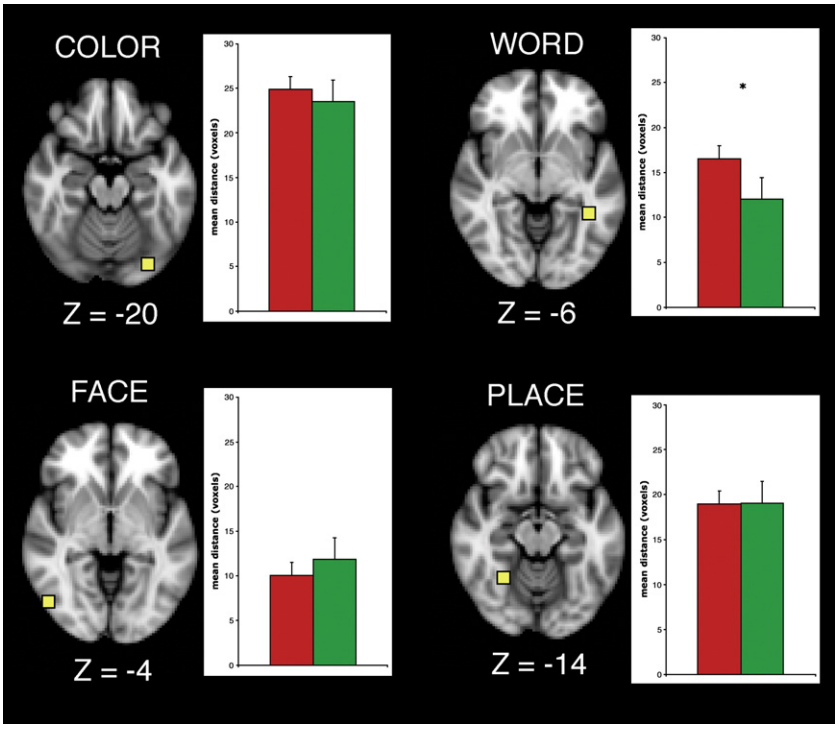

Fig. 1 – Location of common group ROIs and dispersion of subject-specific ROIs for young and old. Common group ROIs are illustrated in yellow, in anatomical space; ROIs did not overlap in either anatomical or functional space. Images are in radiological orientation, R = L. Bar graphs compare peak dispersion for old (red) and young (green) adults. Error bars represent standard error.

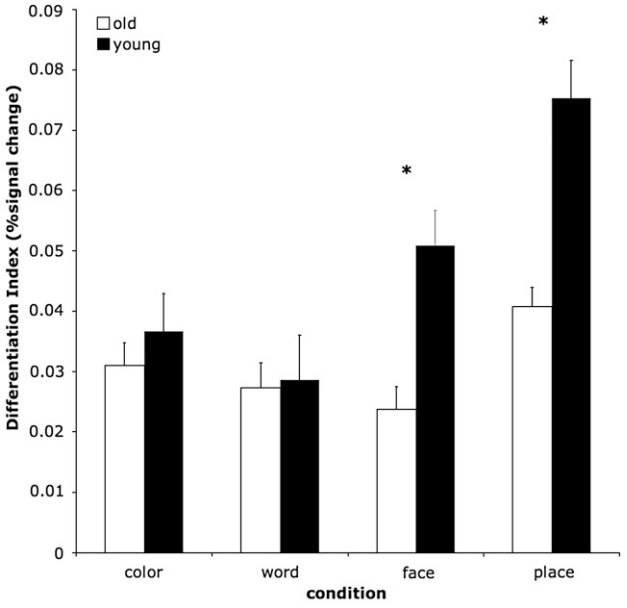

Fig. 3 – Differentiation index as a function of age group. A greater score represents more differentiation, or neural specificity, for a stimulus category in the ventral visual cortex. Error bars represent standard error.

Similar to the results for the color and face localizers, the maximum Z statistic for places for young and old participants was within 6-mm of each other. A 1000-mm^3 common group ROI (125 voxels) for young and old centered on these peaks (MNI: 28, −54, −12) was formed, from which young and old activation patterns were compared. Finally, subject-specific peaks were not more spatially distributed for old adults compared to young in the place condition ($t(76)=.03$; $p>.05$), see Fig. 1. Therefore, an examination of neural specificity in the place group ROI should not bias our results towards finding more neural specificity for young adults.

2.2. *Neural dedifferentiation in the visual cortex*

Neural specificity refers to selectivity of a particular ROI for visual processing of a stimulus category compared to other conditions of stimulus categories. For a detailed description of how dedifferentiation was measured, see the Experimental procedures section and Fig. 2. In short, the presence of neural dedifferentiation was quantified using an index of discriminability, or specificity of response, such that a greater score indicates greater differentiation and a lower score indicates a lack of differentiation, or dedifferentiation.

First, repeated-measures ANOVA was done with differentiation of localized stimulus categories (color, words, faces, and places) as the within-subjects factor and age group (young and old) as the between-subjects factor. There was a significant main effect of differentiation ($F(3,228)=14.95$; $p<.001$), a significant main effect of age ($F(1,76)=16.54$; $p<.001$), and a significant age group × differentiation interaction ($F(3,228)=5.73$; $p=.001$). These results, illustrated in Fig. 3, suggest that despite a main effect of age group, there is significant variation in the amount of differentiation shown for the different localized stimulus categories.

Next, planned comparisons were done to compare age groups on differentiation separately for each localized stimulus condition. Independent samples *t*-tests showed that the young adults were more differentiated in response to faces ($t(76)=3.80$; $p<.001$) and places ($t(76)=5.33$; $p<.001$) compared with old adults. However, both young and old showed similar differentiation for color processing ($t(76)=.80$; $p=.21$) and words ($t(76)=.16$; $p=.44$). The results for the face and place categories support the dedifferentiation hypothesis, however the results for words and color processing suggest that age-

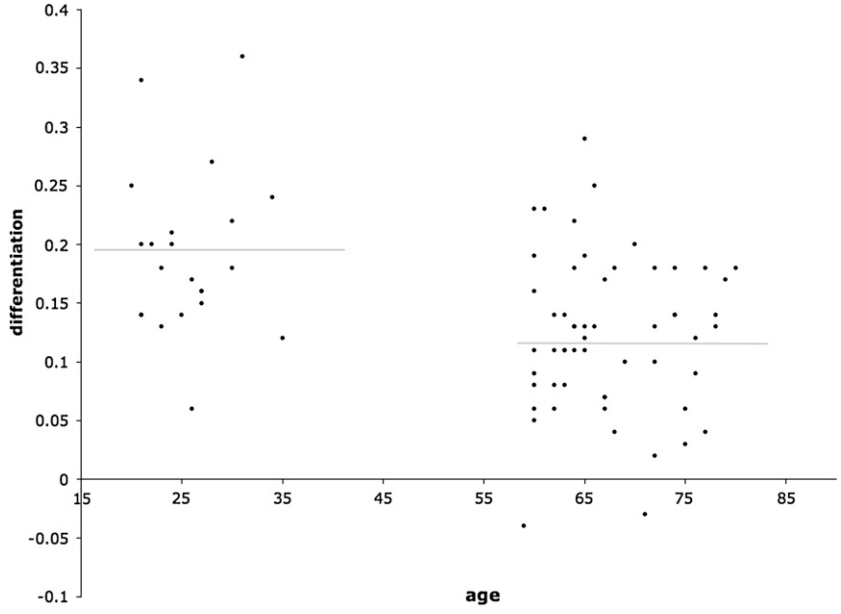

Fig. 4 – Differentiation as a function of age. General differentiation index (summed across condition) plotted as a function of age. Gray bars indicate group means.

related dedifferentiation is not ubiquitous across all stimulus categories.

2.3. *Individual differences and neural dedifferentiation*

A primary application for a quantitative measure of neural dedifferentiation is to provide an individual differences variable of dedifferentiation. We assessed potential moderators of neural dedifferentiation including age, and regional and global gray matter volume.

2.3.1. *Age*

Despite the main effect of age presented above, when only older adults were considered in the analysis, age was not statistically significantly correlated with differentiation for any of the preferred visual processing conditions, or the general differentiation measure (all $p>.10$). This is illustrated in Fig. 4. Even though there were no effects of age within young or old (both $p>.10$), young adults as a group showed more differentiation than old ($t(76)=4.07$; $p<.05$). These results suggest that age may better account for age-related dedifferentiation in the visual cortex in a broader age range of subjects, rather than for the somewhat restricted age range of younger and older adults used in the present study.

2.3.2. *Brain structure*

Regional gray matter volume was not significantly correlated with differentiation for either the young or old adults ($p>.05$). These results are not consistent with a local structure hypothesis, as they suggest that local gray matter volume (as measured by VBM) is not related to neural dedifferentiation. Yet perhaps differentiation depends locally on properties of functional neuronal systems such as neurotrophic factors and neurotransmitter system efficiency that are not measured in a regional structural analysis, where more global structural measures might reflect the structural integrity of a network of brain regions that support neural differentiation.

To assess the contribution of overall gray matter volume on age-related differences in dedifferentiation a general differentiation score, comprised of the sum of differentiation scores for color, word, face, and place, was correlated with a global (whole brain) estimate of gray matter volume. After removing the variance associated with age, results indicated that gray matter volume was significantly positively correlated with general differentiation ($pr(53)=.25$; $p<.05$) for older adults but not for young adults ($pr(18)=.12$; $p>.05$). Fig. 5 plots old adults' total gray matter volumes with their overall differentiation score. These results support the hypothesis that a network of brain regions outside of or including the ventral visual cortex may be important for neural differentiation.

3. Discussion

As predicted, our results are consistent with previous findings that young adults showed more neural specificity in the ventral visual cortex compared with old adults. Our results are novel in demonstrating that while dedifferentiation was shown to be ubiquitous in the sense that it occurred for all older adults regardless of age, dedifferentiation was not shown to be ubiquitous across stimulus categories. Young adults showed more neural specificity for faces and places compared with old adults. However, both young and old adults showed similar neural specificity for color and word processing. We illustrated this using a measure of discriminability to quantify differentiation (converse of dedifferentiation) that

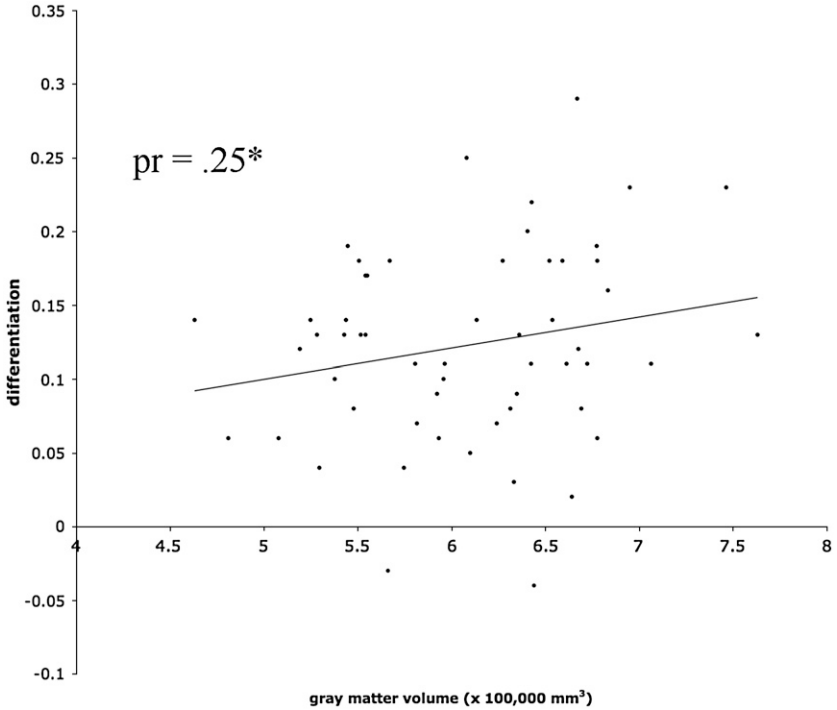

Fig. 5 – Differentiation as a function of gray matter volume. Differentiation is positively correlated with global gray matter volume for older adults.

takes into account both magnitude and variance of brain activation. The differentiation measure provides a quantitative means to examine activation patterns associated with neural dedifferentiation and to directly test theories of behavioral dedifferentiation in cognitive aging literature.

An interesting result that we found based on using this measure was the presence of age-related dedifferentiation for faces and places, but not for colors and words. While we can only speculate, these results are consistent with the right hemisphere hypothesis of aging that proposes age-related cognitive decline affects functions attributed to the right hemisphere to a greater degree than those associated with the left hemisphere (for review, see Dolcos et al., 2002). In the current study, the two conditions that showed age-related dedifferentiation (face and place) were right lateralized in the ventral visual cortex, while the two conditions that did not show age-related dedifferentiation (color and words) were left lateralized (see Fig. 1). Similarly, a meta-analytic review of prefrontal (PFC) brain function by Rajah and D'Esposito (2005), found evidence for age-related dedifferentiation in the right PFC but not in the left. Thus, the results of the current study provide evidence to support the hypothesis that age-related dedifferentiation may be a result of region-specific functional changes in the ventral visual cortex.

Given that age-related neural dedifferentiation was not ubiquitous across visual processing conditions, it is important to identify variables that might moderate the link between aging and neural dedifferentiation. We correlated activation patterns associated with dedifferentiation with age and measures of gray matter volume. Results showed that, after removing the variance associated with age, among the older adults increasing age and decreased regional gray matter volume were not associated with greater neural dedifferentiation. However, those with more global gray matter volume showed less dedifferentiation in the visual cortex.

Furthermore, the general differentiation index should be sensitive to differences in global scaling of activation in the ventral visual cortex. The general differentiation index is the sum of differentiation scores across colors, words, faces and places per individual. If an older participant showed increased activation to a preferred stimulus not only in the preferred ROI, but also across the entire ventral visual cortex, compared with young who showed increased activation to faces only in the preferred stimulus processing ROI, this would result in a low general differentiation score. While there was a main effect of age for general differentiation, for the old adults general differentiation was uncorrelated with age. This suggests that neural dedifferentiation is not a phenomenon that continues to progress with advancing age among older adults (at least within the age range of older adults who participated in our study). This is a somewhat surprising result, however, no studies to date have examined neural dedifferentiation as a function of age in a sample comprised of only older adults. Therefore, examining the trajectory of neural dedifferentiation across a broad age range of middle-aged and older adults, or through a longitudinal design, is an important area of future study.

Also, we believe that our measure of neural specificity would detect age differences in regional response scaling. For example, per individual a high differentiation score could only result from having increased activation to the preferred stimulus within the preferred ROI compared with the non-preferred stimuli. Each person's neural specificity measure for a stimulus category is relative to their own response amplitude across conditions. Therefore differences in regional response scaling across individuals should not affect group differences in the differentiation measure in the present study.

In terms of brain structure, we did not find a significant relationship between functionally co-localized measures of brain structure and differentiation for older adults. However, older adults with more overall gray matter exhibited more neural differentiation, suggesting that the structural integrity of a supporting network of brain regions may play an important role in neural differentiation. While our measure of global brain matter volume is a crude approximation of supporting brain networks, future investigations should expand upon this finding. For example, recent literature has shown that older adults that are cognitively impaired have decreased brain activity in a functional "default mode" network of distinct brain regions (Greicius et al., 2004; Persson et al., 2007). The extent to which differentiation is related to resting state networks and in turn with cognitive efficiency is an important topic for future studies. In addition, earlier research by LaBerge developed a triangular theory of attentional modulation of the ventral visual cortex (LaBerge, 1997, 2002). LaBerge's triangular theory of attention featured cortico-cortical connections between the prefrontal cortices and posterior regions together with cortico-thalamic connections between the thalamus and frontal, and primary and ventral visual regions as a mechanism for functional neuromodulation of sensory perception. The triangular circuit is therefore also a good candidate for future investigation of neural networks involved in differentiation in the visual cortex. Recent advances in multivariate statistical analyses of fMRI activity and high-resolution imaging of structural connectivity (diffusion tensor imaging) will permit sophisticated examinations of functional connectivity in such brain networks in relation to the dedifferentiation theory of aging.

Both an advantage and limitation of the current study is the nature of the passive viewing task. Since participants were instructed only to pay attention to the computer screen, it is unlikely that task difficulty is confounded in our results. However, a limitation of the approach used in our study was a loss of experimental control for the amount of attention paid to the images. In future studies, a surprise recognition test may be able to provide a behavioral measure to examine this. In addition, since one hypothesis of age-related dedifferentiation in the visual cortex is a concomitant decline in visual processing speed (Park et al., 2004), it would also be advantageous to have a measure of processing speed for visually presented images.

Another interesting follow-up to the present study of individual differences in visual processing specificity would be an assessment of brain regions that could potentially act as functional support for visual processing, such as prefrontal brain regions involved in higher order processes of visual attention and perception. In paradigms assessing processes of attention and memory, with performance measures, some researchers have found that differences in the spatial distribution of brain activation can be beneficial for cognitive performance of older adults compared to young (Cabeza et al.,

2002; Reuter-Lorenz and Lustig, 2005). Supporting, or compensatory, brain activation could be the result of any number of factors, including a shift in task-related neural activity to brain regions that are less susceptible to age-related degradation, increase in overall available resources for cognitive processes, strategy differences, greater structural variability in some brain regions for older adults compared with young, or some or all of the above. Given the many potential sources of compensation, in the context of the current study, it would be interesting to determine whether compensatory brain activation in regions outside of the visual cortex change as a function of individual differences or task demands. However, without manipulating the functionality of regions that are potentially compensatory, it would not be possible to determine whether added activation in regions outside of the visual cortex are causally connected with maintenance of visual processing specificity, or are just epiphenomenal. Studies that incorporate cognitive training to assess how brain activation changes as a result of training and improved behavioral performance also provide evidence to interpret the cognitive relevance of age-related differences in activation patterns. For example, Erickson et al. (2007) trained a group of older adults on a dual task paradigm and found that cognitive training resulted in activation patterns that were more similar to young adults. This study points out the importance of longitudinal training studies for understanding the cognitive implications of changes in brain activation patterns with age.

In addition, given that we did not find significant correlations between age and neural dedifferentiation for either young or old, it would be interesting in future studies to assess neural dedifferentiation (1) across a broad age range of subjects that additionally includes subjects of ages 35 through 55 and greater than 80 years, and (2) in different brain regions such as the hippocampus or prefrontal cortices which are more susceptible to age-related structural and functional degeneration. Further examinations in different brain regions and for varying cognitive functions will prove invaluable for characterizing the putative ubiquitous nature of age-related dedifferentiation. Moreover, longitudinal assessments of neural dedifferentiation would permit an analysis of both intra- and inter-individual variance in neural dedifferentiation across the lifespan. Finally, the current study results point out the importance of looking beyond the main effects of age, as well as the possibility that neural dedifferentiation in the visual cortex is not a homogenous phenomenon that continues to progress with advancing age among older adults.

4. Experimental procedures

4.1. *Participants*

Participants were recruited from the local community of Urbana-Champaign, Illinois. Eligible participants had to (1) demonstrate strong right handedness, with a 75% or above on the Edinburgh Handedness Questionnaire (Oldfield, 1971), (2) be between the ages of 18 and 35 for young adults and between 55 and 80 years for older adults (3) score>51 on the modified Mini-Mental Status Exam (mMMSE, (Stern et al., 1987)), a screening questionnaire to rule out potential neurological pathology, (4) score<3 on the Geriatric Depression Scale (GDS) (Yesavage et al., 1983; Sheikh and Yesavage, 1986), (5) have normal color vision (6) have a corrected visual acuity of at least 20/40 and (7) sign an informed consent form.

All participants completed a mock MRI session, wherein participants were screened for their ability to complete an MRI experiment. In separate sessions participants completed a series of structural and functional MRI scans. Prior to MR scanning all participants were tested for visual acuity and (if need be) corrective lenses were provided within the viewing goggles to ensure a corrected vision of at least 20/40 while in the scanner. Participants were compensated for their participation.

In all, 78 participants were included in the present study. There were 56 old adults (40 female) with an average age of 67.36 years (SD=6.09; range 59–80), and 22 young adults (19 females) with an average age of 25.73 years (SD=4.30; range 20–35).

4.2. *Structural MRI protocol*

For all participants, high-resolution T1-weighted brain images were acquired using a 3D MPRAGE (Magnetization Prepared Rapid Gradient Echo Imaging) protocol with 144 contiguous axial slices, collected in ascending fashion parallel to the anterior and posterior commissures, echo time (TE)=3.87 ms, repetition time (TR)=1800 ms, field of view (FOV)=256 mm, acquisition matrix 192 mm×192 mm, slice thickness=1.3 mm, and flip angle=8°. All images were collected on a 3T head-only Siemens Allegra MRI scanner.

4.3. *Functional MRI protocol*

4.3.1. *Procedure*

Visual stimuli were presented with MRI-safe fiber optic goggles (Resonance Technologies, Inc.). Participants completed the localizer scans as part of a larger battery of cognitive paradigms within the scanner.

4.3.2. *Parameters and preprocessing*

For the fMRI protocol, T2* weighted images were acquired using a fast echo-planar imaging (EPI) sequence with Blood Oxygenation Level Dependent (BOLD) contrast (64×64 matrix, 4 mm slice thickness, TR=1500 ms, TE=26 ms, flip angle=60°). A total of 150 volumes were acquired per participant for the color localizer, 220 volumes for the word localizer, and 180 volumes for the face and place localizer (see below for description of localizer scans).

The fMRI data for each participant was preprocessed using FSL version 3.3 (Smith et al., 2004). For all the localizer tasks, images were slice-time corrected, motion-corrected using MCFLIRT (Jenkinson et al., 2002), temporally filtered with a high pass frequency cut-off of 120 s and a low pass cut-off of 9.32 s, and spatially smoothed with a 6 mm full-width half-max 3D Gaussian kernel.

4.4. *Localization procedure and analysis*

Statistical analysis of functional MRI data was carried out using FEAT (FMRI Expert Analysis Tool, http://www.fmrib.ox.ac.uk/analysis/research/feat/) Version 5.1, part of FSL. Higher-

level group analyses were carried out using FLAME (Beckmann et al., 2003).

Specifically, the hemodynamic response to each block for each condition was modeled with a double-gamma HRF function. Note the same high pass temporal filtering that was applied to the data was applied to the general linear model for the best possible match between the model and data. This first level analysis resulted in voxel-wise statistical parametric maps for the entire brain of each individual for separate direct comparisons between 1) color checkerboards and black-and-white checkerboards, 2) words and pseudo-words and letter strings, and 3) faces and buildings. Individual level maps were then registered to the study-specific template appropriate for the following group analysis (young brains were registered to the MNI template, and the average of these MNI registered brains of the young participants in the study formed the young brain study-specific template for the young group analysis; the same process was done for older adults). This was done to minimize the amount of warping during the registration process, and to protect against registration bias between groups. Once individual brains were in a common space for their age group analysis, they were forwarded to separate higher-level mixed-effects group analyses to find areas across participants for each group that were sensitive to color, words, faces, and places. Statistical parametric maps were thresholded at a voxel-wise Z score of 2.33 with a (corrected) cluster-wise threshold of $p<.05$ (Friston et al., 1994; Worsley et al., 1992). Once separate group level analyses were done for young and old, statistical parametric maps for both groups were registered to a common study-specific template of the average brain for all participants in the study (following the procedure outlined for young brains above, but including both young and old brains for all participants). This ensured that statistical peaks for each group level analysis were in the same MNI coordinate space.

4.4.1. *Color localization*

In order to assess perception of color, we presented luminance-matched flashing black-and-white (BW) checkerboards and flashing color (COL) checkerboards at a rate of 8 Hz. Each checkerboard condition was presented in two separate 30-second blocks that alternated with 20-second blocks of fixation baseline. The order of the blocks was BW, COL, BW, COL, and was the same across participants. Participants were instructed to keep their eyes open and to pay attention to the screen. The luminance of both BW and COL checkerboards was equated to ensure that any differences between the conditions were not due to differences in luminance.

Linear contrasts between COL and BW checkerboard conditions were done to isolate regions of cortex sensitive to color processing. For both age groups this resulted in a bilateral cluster of activation spanning the striate and extrastriate visual cortices. The top peak for both age groups was in the ventral region of their respective activation clusters, closest to the V4 and V8 extrastriate regions that have shown to be sensitive to color processing in previous literature (Gegenfurtner, 2003). For comprehensive tables listing peak locations in group clusters and cluster sizes, please see supplementary information. Group localized clusters for color processing were used as functionally defined ROIs from which subject-specific Z statistic peaks were located. Subject-specific 1000-mm^3 ROIs (125 voxels in high-resolution MNI space) were centered on subject-specific peaks to form subject-specific ROIs for color processing. The location of subject-specific peaks was also used to assess inter-individual spatial variability in category specific neural response. Subject-specific peaks were located in native space and the resulting coordinates were transformed into MNI space corresponding to the study-wide MNI template. This was done to ensure coordinates for subject-specific peaks all referred to a common MNI space so we could directly compare them.

4.4.2. *Word localization*

To localize word and letter-sensitive brain regions we presented 30-second blocks of words, pseudo-words, and letter strings. As in the color localizer, each condition in the word localizer task was presented separately in two 30-second blocks that alternated with 20-second blocks of fixation baseline. The order of the blocks was WORD, PSEUDO, STRING, WORD, PSEUDO, STRING, and was the same across participants. Each block consisted of 20 unique stimuli that were each presented for 1 s with a 500 ms fixation between each word presentation.

Linear contrasts between words and the conjunction of pseudo-words and letter strings were done to isolate regions of cortex sensitive to word processing. No clusters of activation were found for the comparison of words greater than pseudo-words and letter strings for either young or old adult group analyses. This is consistent with recent evidence that the previously described visual word form area (VWFA: Dehaene et al., 2002) in the left ventral visual cortex (approximate MNI coordinates: −43, −54, −18) is equally responsive to words, pseudo-words and semantic symbols (Reinke et al., 2008; Kronbichler et al., 2007). However, previous literature and a recent meta-analysis of word-related brain activity (Jobard et al., 2003) report consistent evidence supporting the claim that activation to words can be reliably localized to the left posterior inferior temporal region. Based on these findings, a mask of the left posterior inferior temporal region served as a search space for peaks within the Z statistic map for each subject for the contrast between words and the conjunction of pseudo-words and letter strings. As described above, subject-specific ROIs (125 voxels) were formed around subject-specific statistical peaks, from which young and old activation patterns were compared (see Fig. 1).

4.4.3. *Face and place localization*

To localize face and place sensitive regions of cortex we presented three 20-second blocks of faces and buildings that alternated with 20-second blocks of luminance-matched scrambled images (taken from the face and building stimulus set) as the baseline condition. The order of the blocks was FACE, PLACE, FACE, PLACE, FACE, PLACE, with scrambled images of the face and house stimulus blocks following each block respectively. Stimulus order was the same across participants. Each block consisted of 20 unique black-and-white images (controlled for luminance and dimension) that were each presented for 1 s with no inter-trial fixation cross. Blocks of trials were convolved with a double-gamma HRF function, and linear contrasts were done to identify brain regions sensitive to processing faces (face>building) and places (building>face).

It is important to note that the comparison of faces and places is not a clear conceptual comparison to isolate regions of cortex for face>all non-face stimuli. However, the contrast of face>scrambled images does not provide a comparison against complex visual processing. Therefore, to optimally localize regions of interest for the face condition, a face>place contrast was used to define a cluster of interest that was consistent with previous face processing literature. The resulting cluster was used to mask the statistical maps for the face>scrambled images baseline comparison, to localize peaks of activation for face processing. For comprehensive tables listing peak locations in group clusters and cluster sizes, please see supplementary information. The results from the contrast of faces and buildings within the young and old adult analyses showed unilateral clusters of activation in the right fusiform gyrus that correspond with previously cited regions (Fusiform Face Area: FFA) of face selective response (see Fig. 1) (Kanwisher, 2000; Downing et al., 2006). Subject-specific ROIs for face processing were generated as described above for the color localizer.

The comparison of places to faces suffers the same conceptual limitation as noted for face localization above. Therefore, the same procedure was done for places as described above for faces, for localizing regions of activation for place processing. Linear place>face contrasts were done to localize a significant cluster of activation consistent with previous literature on place processing. The resulting cluster was used to mask the statistical maps for the place>scrambled images baseline comparison, to localize peaks of activation for place processing. The results from the contrast of buildings and faces within the young and old adult analyses showed bilateral clusters of activation in the left and right parietal and parahippocampal regions. The peaks for the most place sensitive regions of cortex were found more medial than activation to either faces or words, and correspond with previously cited regions (parahippocampal place area: PPA) for place selective response (see Fig. 1) (Epstein and Kanwisher, 1998; Downing et al., 2006). For comprehensive tables listing peak locations in group clusters and cluster sizes, please see supplementary information. Subject-specific ROIs for place processing were generated as described above for the color localizer.

In sum, a procedure was used to localize both a common group ROI for old and young and subject-specific ROIs for color, words, faces and places. Although no common group ROI for old and young resulted from our word localizer analyses. Average percent signal change was extracted from the common group and subject-specific ROIs for each localizer condition versus baseline for both the preferred and non-preferred stimulus categories. This was done to (1) confirm that the common group and subject-specific localized ROIs were most sensitive to the hypothesized preferred stimulus category, (2) to assess age-related differences in stimulus-specific neural specificity, and (3) to assess spatial variability of subject-specific ROIs.

4.5. *Measuring neural specificity*

4.5.1. *Differentiation index*

Some human studies have quantified neural dedifferentiation as the number of activated voxels for non-preferred stimuli that overlap with preferred-stimulus regions (Park et al., 2004; Payer et al., 2006). That is, increased dedifferentiation is indexed by increased overlap of supra-threshold voxels for non-preferred stimuli within areas of activation for the preferred stimulus category. While this approach has advantages, there are also several problems with this metric. Most importantly, threshold artifacts bias its determination of "activated" voxels for one group compared to another (Zarahn et al., 2007). Second, it implies that neural dedifferentiation be measured by qualitative spatial overlap rather than by the magnitude of functional overlap. That is, an index of neural specificity should be independent of threshold artifact and distinguish those individuals that showed maximal sensitivity to the localized stimuli while showing minimal activity to the other localizer conditions. Furthermore, older adults have been shown to exhibit greater variability in response amplitude across time than younger adults (Huettel et al., 2001). This suggests that variability of BOLD response should also be considered in a measure of neural specificity that will be used to compare young and old adults.

Therefore, in the present study the presence of neural dedifferentiation was quantified using an index of discriminability, or differentiation, such that a greater score indicates greater differentiation and a lower score indicates a lack of differentiation, or dedifferentiation.

The index measures neural differentiation as the average activation (percent signal change) to the preferred stimulus within the preferred stimulus-localized ROI minus the average activation to the non-preferred stimulus conditions within the preferred stimulus-localized ROI, divided by the average standard deviation of the response amplitude for preferred and all non-preferred stimulus conditions within the preferred stimulus-localized ROI (adapted from Afraz et al., 2006 and Grill-Spector et al., 2007), see Fig. 2.

The measure was computed for each individual and served as an individual differences variable representing neural specificity for the preferred stimulus within the ventral visual cortex relative to the other localizer conditions. The sum of differentiation scores across stimulus categories generated a measure of general differentiation.

4.6. *Spatial dispersion of peak activation*

The distance between subject-specific ROIs and the common group Z statistic peak was calculated using the 3-dimensional distance formula ($D=[(x_1-x_2)^2+(y_1-y_2)^2+(z_1+z_2)^2]^{1/2}$). Specifically, the distance between the central coordinates for each participant's subject-specific ROI and the coordinates of the maximum Z statistic for the common group ROI for old and young was computed for each stimulus category.

4.7. *Structural brain analysis*

We used an optimized voxel-based morphometry (VBM) technique (Ashburner and Friston, 2000; Good et al., 2001) to assess the extent to which local and global volume differences predict neural dedifferentiation within older adults. Our primary dependent measures for VBM were gray matter partial volume maps, derived from high-resolution magnetic resonance images that were standardized to a study-specific reference template in MNI space. The optimized VBM method improves upon earlier

VBM procedures in that a study-specific template, or the average brain of study participants, is generated and used as the reference image for whole head and ROI registrations. First, all the brains were stripped of extracranial matter (e.g., skull, eyes) using an accurate and robust deformable model algorithm (Smith, 2002). These skull-stripped brains were registered to a standardized stereotaxic space (152 T1 MNI, Montreal Neurological Institute) using a robust 12-parameter affine transform (Jenkinson et al., 2002). Standardized skull-stripped images were then averaged to form one composite image representing the average brain of our sample population. For all VBM analyses we used FSL 3.3 (Smith et al., 2004). For extensive documentation of the VBM procedure used here, see Erickson et al., 2005. We used a 6 FWHM smoothing kernel for this data. Estimates of local brain structure within subject-specific and the common group defined ROIs were extracted from gray matter partial volume estimate maps for each subject. The resulting mean partial volume estimates represented average gray matter volume estimates within stimulus-localized regions of cortex for subject-specific peaks in addition to the common group ROI for young and old. Global gray matter volume estimates were derived from whole-brain initial segmentation images and represent the volume (in mm^3) of voxels classified as gray matter (Zhang et al., 2001).

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Disclosure statement

Appropriate approval and procedures were used for the use of human subjects in this research. All authors have reviewed the contents of the manuscript being submitted, approve of its contents and validate the accuracy of the data. None of the authors have actual or potential conflicts of interest related to this work.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.brainres.2008.09.051.

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