**Causes and consequences of dedifferentiation in the aging brain**

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# Abstract

Cognitive performance declines across the adult lifespan. According to the dedifferentiation hypothesis of cognitive aging, age-related impairments in cognitive function stem from reductions in the fidelity of neural representations. However, behavioral tests of this hypothesis have yielded mixed results. Thus, the present research sought to explore age-related dedifferentiation using pattern classification of neural activity, which may yield a more direct, and more reliable, measure of representational fidelity. Three studies examined age differences in the fidelity of the neural representations of visual stimuli, motor actions, and cognitive task sets, respectively. Study 1 showed that multi-voxel activation patterns evoked by presentation of face and house stimuli were less distinctive in older adults than in young adults. This pattern was observed both in the ventral visual cortex, which is thought to be specialized for the perception of visual category information, and throughout a network of regions implicated in object perception. No regions showed greater distinctiveness in older adults than in young adults, and the spatial pattern of category information was similar across age groups, suggesting that older adults do not compensate for low-fidelity representations in visual cortex by forming higher-fidelity representations elsewhere in the brain. Study 2 extended these results to the domain of motor control, using multi-voxel pattern analysis to distinguish between left- and right-hand finger movements. Older adults showed reduced distinctiveness throughout a network of regions related to motor representation and control; again, no regions showed greater distinctiveness in older adults. Study 3 further investigated age differences in neural representations in the context of verbal and spatial working memory tasks. Results from memory encoding and retrieval were consistent with Studies 1 and 2, with reduced discrimination of verbal versus spatial information in older adults. In contrast, results from working memory maintenance showed that representational fidelity was decreased in older adults at high levels of task demand but increased in older adults at low levels of demand. Overall, results from perceptual and motor tasks were consistent with the dedifferentiation hypothesis, while results from memory maintenance were more consistent with compensation-related accounts of cognitive aging. These results suggest that both dedifferentiation- and compensation-based accounts can explain some phenomena, but that neither category of theory can offer a comprehensive account of age differences in neural representation. Future research should investigate the generalizability of the present results across analysis methods, cognitive tasks, and participant populations. Ongoing studies in the lab will also continue to explore the neurochemical origins of age-related changes in neural specificity.

# Chapter 1: Introduction

Aging is associated with pervasive deficits in perceptual and cognitive performance, ranging from low-level perception (Spear, 1993) and motor control (Seidler et al., 2010) to working memory and executive control (Park et al., 2002). Although these changes are accelerated in conjunction with age-associated disorders, they are also evident even in the absence of any detectable pathology (Salthouse, 2009). Nevertheless, while older adults show poorer performance than young adults on average, some older adults perform as well as young adults (e.g., Cabeza et al., 2002). Indeed, some studies suggest that performance among older adults is more variable than among young adults (Nelson and Dannefer, 1992). Why does cognitive performance decline in many, but not in all, older adults?

According to a computational model developed by Li and colleagues (2001), age-related cognitive impairment is at least partly attributable to age differences in the fidelity of neural representations. This model posits that impaired dopaminergic function reduces neural signal-to-noise ratio (SNR) in old age. Striatal and cortical dopamine systems decline across the adult lifespan. Densities of D1 receptors (Wang et al., 1998), D2 receptors (Ichise et al., 1998), and the dopamine transporter (Erixon-Lindroth et al., 2005) in the caudate and putamen are estimated to decline by 5-10% per decade. Aging is also associated with declining dopamine receptor availability in the cortex, with particularly dramatic declines in frontal regions (Kaasinen et al., 2002). Further, individual differences in dopaminergic function predict cognitive performance independent of age (Volkow et al., 1996), and controlling for these differences reduces or eliminates the relationship between aging and cognition (Bäckman et al., 2000). Li and colleagues proposed that impaired dopaminergic communication in old age has the effect of reducing neural gain, such that an equivalent change in input signal evokes a

smaller change in neural activity in older adults than in young adults. Thus, smaller neural signals are more easily swamped by noise in old age.

Li et al. further propose that reductions in SNR result in relatively similar neural representations of different mental states, from visual percepts to motor actions to higher-order executive representations. When SNR is high, different mental states elicit distinct patterns of activation across a population of neurons. When SNR is low, different states elicit relatively similar activation patterns. This loss of representational distinctiveness could give rise to various impairments in performance, disrupting the encoding of different perceptual states, memory traces, or task goals. Indeed, Li and colleagues (Li et al., 2000) have used computational modeling to show that reduced neural gain could explain poorer performance across a range of cognitive tasks for which older adults show impairments, including paired associate learning and resistance to proactive interference. While this model makes similar predictions to earlier neural noise (e.g., Welford, 1981) and common cause (e.g., Christensen et al., 2001) accounts of cognitive aging, it makes clearer predictions about the neural mechanisms of age-related cognitive decline. In particular, Li's computational model of age-related dedifferentiation attempts to link neurochemical, computational, and behavioral aspects of age-related cognitive impairment.

This computational model offers a compelling, cross-level account of age-related cognitive change. However, the mere fact that a computational model provides a good fit with empirical data does not show that the model corresponds to reality (Roberts and Pashler, 2000). Evidence consistent with one model may be consistent with many others. One distinguishing prediction of Li's dedifferentiation model is that older adults will not only show impaired cognitive performance; they will further show more similar performance across stimulus categories and cognitive domains. In particular, the model draws support from a variety of behavioral studies arguing that correlations among cognitive abilities increase from young adulthood into old age. An early study by McHugh and Owens (1954) showed that the first component of a principal component

analysis of cognitive tests explains more variance in older adults than in young adults, suggesting that the dimensional structure of cognitive ability grows more sparse in old age. Similarly, Lienert and Crott (1964) reported that correlations between measures of fluid intelligence increased across adult age. More recently, Li and colleagues (2004) and de Frias and colleagues (2007) have also reported age-related increases in the correlations and decreases in dimensionality among cognitive measures.

However, behavioral studies of the dedifferentiation hypothesis have long been dogged by methodological challenges and inconsistent findings. Studies of ability dedifferentiation vary with respect to the number and identity of cognitive tests, the definition of age groups, and the choice of analytic approach. Thus, it is perhaps unsurprising that many reports have failed to replicate prior findings of dedifferentiation in old age. A cross-sectional study by Cunningham (1980) found no evidence for age differences in the factor structure of fluid intelligence. Similar cross-sectional results have been reported by Park and colleagues (2002) and by Tucker-Drob and Salthouse (2008). In fact, Tucker-Drob and Salthouse reported that the few differences in inter-ability correlations that they found indicated greater distinctiveness (i.e., lower correlations) among older adults than young adults. Longitudinal studies have also failed to support the dedifferentiation hypothesis. Anstey and colleagues (2003) found that correlations among cognitive tests were stable across age for both longitudinal and cross-sectional analyses; Zelinski and Lewis (2003) also found no evidence for longitudinal change in the structure of intelligence. Finally, Bickley and colleagues (1995) found that correlations among cognitive abilities were stable from age 6 to age 79, arguing that the differentiation of intelligence is intact in both old age and in childhood.

Altogether, behavioral tests of the dedifferentiation hypothesis have proven inconclusive. Results vary widely across studies, with some reports showing increased inter-task correlations with increasing age, some showing no age-related change, and others showing increased ability differentiation in old age. Further, while these studies

vary in terms of behavioral assessments, sampling procedures, and designs (e.g., cross-sectional vs. longitudinal), no clear pattern separates the studies that have provided support for age-related ability dedifferentiation from the studies that have not. Notably, while most studies of dedifferentiation acknowledge previous experiments that have yielded contradictory results, most studies offer little speculation about the origins of these differences. Such inconsistencies may stem from the fact that the measures used by these studies are far removed from the underlying phenomena of interest. Li's model of age-related dedifferentiation posits a complex causal chain, in which age-related changes in neuromodulation indirectly bring about lifespan differences in cross-subject correlations between tasks. Disagreements among studies of dedifferentiation suggest that different studies are measuring different phenomena.

Physiological studies in animals suggest that neural measures may offer a more direct, and more reliable, index of age differences in representational fidelity than the behavioral measures described above. For example, Leventhal and colleagues (Leventhal et al., 2003; Schmolesky et al., 2000) have reported that individual neurons in visual cortex are less sensitive to simple visual features (such as orientation and direction of motion) in older macaques, relative to young adult macaques. These authors have documented comparable findings across visual modalities (Liang et al., 2010; Wang et al., 2005), and in cats (Hua et al., 2006) and rats (Wang et al., 2006). These results offer consistent support for the dedifferentiation hypothesis, without the ambiguity associated with the highly indirect behavioral measures used to study ability dedifferentiation.

While the single-cell recording measures used by Leventhal and colleagues cannot (ethically) be used in humans, neuroimaging measures may offer an acceptable compromise between proximity to the phenomena of interest and practicality. Several recent fMRI studies have provided evidence in support of age-related neural dedifferentiation. In contrast to behavioral studies of ability dedifferentiation, neuroimaging studies focus on intra-individual comparisons of the neural responses

evoked by different task conditions. For example, Park and colleagues (2004) argued that regions of the ventral visual cortex that are highly specialized for particular stimulus categories in young adults become less specialized in old age. These investigators presented young and older adults with images of faces, houses, pseudo-words, chairs, and scrambled images while functional magnetic resonance imaging (fMRI) data were acquired. Voxels in the ventral visual cortex exhibiting peak responses to each of the four stimulus categories were then identified for each subject. By definition, these peak voxels showed strong responses to their preferred category in both young and older adults. In young adults, these voxels responded weakly to non-preferred categories. In older adults, in contrast, the difference in response to preferred and non-preferred categories was markedly reduced. Park and colleagues (2004) interpreted these findings as direct neural support for the dedifferentiation hypothesis. Voss and colleagues (2008) obtained analogous findings using a larger sample size, and used voxel-based morphometry (VBM) measures to show that age differences in the distinctiveness of stimulus-evoked activation remain significant when controlling for individual differences in gray matter volume. Finally, Payer et al. (2006) replicated these findings in the context of a working memory task, showing that neural responses recorded during the encoding of face and house images were less distinctive in older adults.

However, recent methodological advances in the analysis of functional neuroimaging data raise new questions about the meaning of these results. In particular, recent studies argue that conventional univariate analytic procedures focusing on mean regional activation often fail to detect information encoded in multi-voxel activation patterns (Haxby et al., 2001; Kamitani and Tong, 2005). So-called multi-voxel (or multivariate) pattern analysis (MVPA) is argued to offer higher sensitivity than conventional measures for two reasons (Norman et al., 2006). First, univariate methods threshold the statistical significance of each voxel individually, meaning that information from voxels that do not pass the thresholding criteria is lost. In contrast, MVPA can incorporate information from voxels that do not show significant responses according to

single-voxel significance testing. Second, conventional methods smooth or average activation estimates across spatially proximal voxels. Thus, if nearby voxels show different or opposing relationships with experimental conditions, information they might provide about those conditions is attenuated by spatial averaging. In contrast, most MVPA studies do not apply spatial smoothing, preserving information that may be encoded in fine-grained spatial activation patterns.

Thus, the univariate measures used by Park and colleagues (2004) may have understated the amount of category information encoded in the aging brain. Perhaps, for example, more information was lost from sub-threshold voxels in older adults than in young adults; or perhaps spatial averaging attenuates decoding of experimental conditions more sharply in older adults. In either case, conventional univariate analysis could underestimate the quantity of information about experimental conditions encoded in multi-voxel activation patterns in old age. Alternatively, the univariate measures used in previous studies may have failed to detect pattern-encoded information in young adults, underestimating the true age difference in representational differentiation. Thus, previous neuroimaging studies of age-related dedifferentiation may have either underestimated or overestimated true age differences.

Inconsistencies among behavioral studies of ability dedifferentiation suggest that methodological differences, such as choice of tasks studied, may have powerful consequences with regard to research outcomes. Furthermore, previous theorizing on age-related dedifferentiation encompassed a wide range of intellectual abilities, including motor control and auditory function as well as the higher-level cognitive constructs included under the rubric of fluid intelligence. Thus, both to assess potential inconsistencies across perceptual and cognitive domains and to provide a thorough test of the dedifferentiation hypothesis, it is critical to examine a broad selection of tasks. The small complement of previous studies on age-related neural dedifferentiation have focused on high-level vision, leaving open the possibility that their results reflect a more constrained phenomenon than the widespread change in neural representations posited

by the dedifferentiation hypothesis. And while Payer and colleagues (2006) have studied age-related neural dedifferentiation during a working memory task, this study did not jitter the timing between the encoding, maintenance, and recall phases of the task, precluding rigorous analysis of each individual task phase.

The present research sought to address these limitations and gaps in understanding. Specifically, the present studies investigated putative age differences in the fidelity of neural representations. In contrast to previous behavioral studies of ability dedifferentiation, which have yielded mixed results, these studies used fMRI to achieve relatively direct measures of the neural responses evoked by different perceptual and cognitive states. In addition, in contrast to previous neuroimaging studies, which have focused on univariate metrics of regional brain activation, these studies took advantage of more sensitive analytic procedures that extract information encoded in multi-voxel activation patterns. Finally, these studies examined age-related dedifferentiation across multiple cognitive modalities, including high-level vision (Study 1), motor control (Study 2), and representations of higher-level cognitive tasks (Study 3).

In addition, the present studies also sought to shed light on competing accounts of neuro-cognitive aging. While the dedifferentiation hypothesis advanced by Li and colleagues (2001) focuses on neural and cognitive impairment in old age, alternative accounts of cognitive aging emphasize the ability of the aging brain to compensate for impairment. Previous studies have argued that some age differences in neural activation reflect compensation for underlying impairments. For example, Cabeza and colleagues (2002) argued that increased bilateral activation in old age reflects adaptation rather than impairment: older adults with more bilateral activation also showed improved memory performance. A more nuanced view is offered by the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH), which predicts that age differences in neural activation should vary with task demands (Reuter-Lorenz and Cappell, 2008). This account argues that older adults must engage more neural resources than young adults for equivalent levels of task demand, leading

to increased activation among older adults at low levels of task demand. Thus, older adults reach a resource ceiling earlier than young adults, leading to reduced activation at high levels of demand. The present studies also sought to compare the predictions of dedifferentiation and compensation models of cognitive aging. In particular, analyses investigated (1) whether older adults encoded representations of task information in regions that did not carry this information in young adults, and (2) whether age differences in neural representations showed interactions with task demands.

Note: Studies 1, 2, and 3 have previously been published and are included here in full as Chapters 2, 3, and 4, respectively.

# Chapter 2: Age differences in neural distinctiveness revealed by multi-voxel pattern analysis

## *Introduction*

Current models of aging argue that different cognitive and neural processes become more similar in old age, a phenomenon referred to as dedifferentiation. This term has been applied to patterns of cognitive aging observed across a range of research methods, including behavioral, neuroimaging, and computational modeling approaches. Behavioral studies have documented increased intercorrelations among perceptual and cognitive abilities in older adults (Baltes and Lindenberger, 1997; Li et al., 2004; Lindenberger and Baltes, 1994). Such results have been hypothesized to reflect a global decline in the integrity of the aging brain. The term dedifferentiation has also been applied to a ubiquitous finding in the cognitive aging literature: bilateral activation in older adults during tasks that evoke unilateral activation in younger adults (Cabeza, 2002; Dolcos et al., 2002; Reuter-Lorenz and Lustig, 2005). This additional recruitment has been hypothesized by different groups to reflect (1) compensation for age-related declines in neural resources (e.g., Cabeza et al., 2002) or (2) impaired neural processing (e.g., Duverne et al., 2009). Finally, dedifferentiation also refers to computational modeling work that links age-related performance declines to reduced distinctiveness of neural representations (Li et al., 2001; Li and Sikström, 2002). Consistent with this view, work from our lab and others shows that regional specialization within the ventral visual cortex (VVC) for different visual objects declines in old age (Chee et al., 2006; Park et al., 2004; Payer et al., 2006; Voss et al., 2008). The present study focuses on this variety of age-related dedifferentiation.

In this study, we reanalyzed the data from a previous report (Park et al., 2004) to address three novel questions about age-related dedifferentiation. First, we used multi-voxel pattern analysis (MVPA) to measure age differences in the distinctiveness of neural representations in the VVC. Following Li and Sikström (2002), we define a neural representation of a stimulus as the pattern of neural activity evoked by that stimulus; two neural representations are said to be distinctive if one can be distinguished from the other. Previous studies of neural dedifferentiation in visual cortex have focused on age differences in average regional activation (Grady et al., 1994; Park et al., 2004). However, these measures may not capture information encoded across multiple voxels within a region: patterns of activation that cannot be discriminated by univariate analysis may be discriminable by multivariate techniques (Haynes and Rees, 2006; Norman et al., 2006). Thus, we reasoned that MVPA would provide a more sensitive index of age differences in neural distinctiveness than measures used in previous work.

Second, we predicted that age-related dedifferentiation would extend beyond the visual cortex. Recent methodological advances have extended MVPA to map local changes in the distinctiveness of neural activation patterns throughout the brain using a multivariate searchlight procedure (Kriegeskorte et al., 2006). This method yields a voxel-by-voxel map of neural distinctiveness. Previous studies using univariate statistics have focused on brain regions in which the average response exceeded an arbitrary statistical criterion. In practice, these criteria have restricted analysis to the visual cortex (Grady et al., 1994; Park et al., 2004; Payer et al., 2006; Voss et al., 2008). However, multi-voxel activation patterns in subthreshold regions can also provide information about visual stimulus categories (Harrison and Tong, 2009; Serences et al., 2009). Thus, we used a multivariate searchlight analysis to measure age differences in neural distinctiveness throughout the brain.

Finally, we used MVPA to investigate the possibility that older adults compensate for altered processing in sensory cortex (Park et al., 2004). We asked whether older adults were able to increase the distinctiveness of multi-voxel activation patterns by (1)

distributing stimulus codes across larger numbers of voxels in the visual cortex or (2) engaging brain regions outside the visual cortex. Previous studies of compensation that rely on univariate analysis often yield ambiguous results: age differences in overall activation in frontal areas have been hypothesized to reflect both compensation and impairment and are difficult to interpret (Reuter-Lorenz and Lustig, 2005). In contrast, MVPA measures the information present in patterns of neural activation (Kriegeskorte et al., 2006), simplifying the interpretation of age differences. If neural distinctiveness is reduced in older adults, we can conclude that activation patterns in these subjects convey relatively little information; if older adults exhibit enhanced distinctiveness, we can conclude that their activation patterns convey more information than those of younger subjects. We used both region-of-interest and whole-brain comparisons to assess compensation among older adults.

## *Materials and methods*

### Participants

Thirteen younger adults (age range 18 to 28 years; mean age 20.8 years; seven female) and 12 older adults (age range 64 to 79; mean age 69.9 years; seven female) were tested. All participants were right-handed and had 20/40 vision or better; participants who required vision correction wore corrective lenses in the fMRI scanner. Participants were also screened for disease, major depression, and artificial lens implants. Further details of the sample can be found in the original report of these data (Park et al., 2004).

### Experimental design

Participants viewed static images while fMRI data were acquired. Images were drawn from four categories: faces, houses, pseudo-words, and chairs. Participants also viewed control images generated by phase-scrambling images from each category.

Stimuli were presented in three runs. Each run contained three 20-s blocks of each stimulus category, presented in pseudorandom order. Each block included 10 images from the same category presented for 1500 ms each, followed by a 500-ms inter-trial interval. Participants were instructed to view and try to remember each image. No additional tasks were given during scanning.

## MRI acquisition

All participants were tested in a GE Signa 3T scanner. Neural activity was estimated based on the blood oxygenation level-dependent (BOLD) signal using a spiral acquisition sequence (2000 ms repetition time, 30 5-mm axial slices, 24-cm field of view, 30-ms echo time, 90° flip angle). These acquisition parameters yielded an in-plane resolution of 3.75 by 3.75 mm. High-resolution T1-weighted images were collected in 30 5-mm-thick axial slices parallel to the anterior commissure-posterior commissure line.

## Data analysis

Data were preprocessed using SPM5 (Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk). All subsequent analysis was carried out using custom software implemented in MATLAB (MathWorks, Inc., Natick, MA) and the R statistical computing language.

## Preprocessing

Functional data were corrected for differences in slice time acquisition and realigned to the first volume using SPM5. No normalization, spatial smoothing, or other transformation was applied before multivariate analysis (Haxby et al., 2001).

## Multi-voxel pattern analysis

We used multi-voxel pattern analysis (MVPA) to test the hypothesis that patterns of neural activation evoked by different visual stimuli become less distinctive in old age. Following Haxby and colleagues (2001), we applied MVPA to individual subject data; results were subsequently averaged within age groups. First, we estimated the neural response to each category relative to phase-scrambled control images using the General Linear Model (Friston et al., 1995). Category-evoked activation was estimated separately for each of the three experimental runs. Within each run, the mean activation across all categories was subtracted from each category-evoked activation map (Haxby et al., 2001). Next, we compared within- and between-category correlations across activation maps for all pairs of categories and all pairs of runs. Neural distinctiveness was defined as the difference between the mean within- and between-category correlations, averaged over all such pairwise comparisons (Williams et al., 2007). As a difference between two correlation coefficients, this measure has a theoretical range of 2 to -2. In contrast to the univariate analysis methods used by previous studies of age-related dedifferentiation (Grady et al., 1994; Park et al., 2004), which focus on changes in average regional activation, MVPA reveals fine-grained differences in the distinctiveness of activation patterns (Norman et al., 2006).

## Region-of-interest analysis

The ventral visual cortex (VVC) is specialized for the processing of object form and identity. Patterns of fMRI activation within the VVC reliably discriminate between different visual categories (Haxby et al., 2001). Therefore, we measured age differences in the distinctiveness of distributed category representations within this region. Regions of interest were constructed in two steps (described in further detail below). First, we defined an anatomical mask of the VVC for each subject based on his or her high-resolution structural scan. Second, we selected voxels within each subject's anatomical mask that showed peak responses to visual object categories. Thus, ROIs were

constructed using both anatomical and functional criteria, independently for each subject.

We first constructed single-subject anatomical masks of the VVC that included the parahippocampal gyrus, the inferior temporal gyrus, and the portion of the fusiform gyrus anterior to the anterior occipital sulcus (Park et al., 2004). Next, we identified the voxels within these masks that showed the most robust responses to objects relative to scrambled images. For each subject, we ranked VVC voxels according to their absolute *t*-values for this contrast. The sensitivity of MVPA varies with the number of voxels included in the analysis (e.g., Spiridon and Kanwisher, 2002). Thus, we defined regions of interest (ROIs) comprising the 2, 4, 8, 16, 32, 64, 128, 256, and 512 peak-activated voxels. These voxels were not required to be spatially contiguous. Finally, we used MVPA to measure the distinctiveness of stimulus-evoked activation patterns within each ROI (see Multi-voxel pattern analysis). To maintain independence between voxel selection and pattern classification, we used different runs to define masks and to measure neural distinctiveness. Definition of the overall VVC region was based on anatomical scans and therefore independent from other analysis.

To test the generality of results from the regions described above, we also defined a set of ROIs for each of the four stimulus categories comprising the 2 through 512 voxels that showed the strongest responses to that category. Finally, we also analyzed responses across the entire anatomically defined VVC region.

## Searchlight analysis

We used a multivariate searchlight approach to map age differences in distributed object codes across the brain (Kriegeskorte et al., 2006). For each voxel in the brain, we measured the distinctiveness of visual activation patterns within a 10-mm-radius sphere centered on that voxel (see Multi-voxel pattern analysis). Thus, the value at each voxel

describes the degree to which patterns of activation in the local neighborhood of that voxel differentiate among different stimuli. In this way, we derived a whole-brain map of category distinctiveness for each participant. To permit inter-subject comparisons, these maps were spatially normalized using high-resolution T1-weighted images from each participant. These normalized maps were then entered into a second-level analysis to compare neural distinctiveness among younger and older adults. Random-effects *t*-maps were thresholded at $p < .001$ (uncorrected for multiple comparisons) with an extent threshold of 20 contiguous voxels (Buckner et al., 2000; Cabeza et al., 2002; Huettel et al., 2001; Park et al., 2003). All activation coordinates are reported in MNI space.

## Global correlation analysis

Our region-of-interest and searchlight analyses provide information about local differences in category distinctiveness between younger and older adults. However, these techniques are uninformative with respect to possible age differences in the distribution of category representation across the brain. To assess age differences in the global distribution of category coding, we measured the relationship between neural distinctiveness in older and younger groups across all voxels in the brain. Unlike the ROI and searchlight methods described above, this analysis takes into account the distinctiveness scores from all brain voxels simultaneously. We first computed whole-brain maps of neural distinctiveness for each subject (see Searchlight analysis) and averaged these maps separately for younger and older participants. Next, we correlated the average distinctiveness scores among young participants with the average distinctiveness scores among older participants across all voxels. This technique resembles the Brinley plot (Brinley, 1965), long a staple of cognitive aging research.

## *Results*

## *Region-of-interest analysis*

Younger and older adults showed no differences in the size of the anatomically defined ventral visual cortex ROI ($t(23) = .31$, $p=.77$).

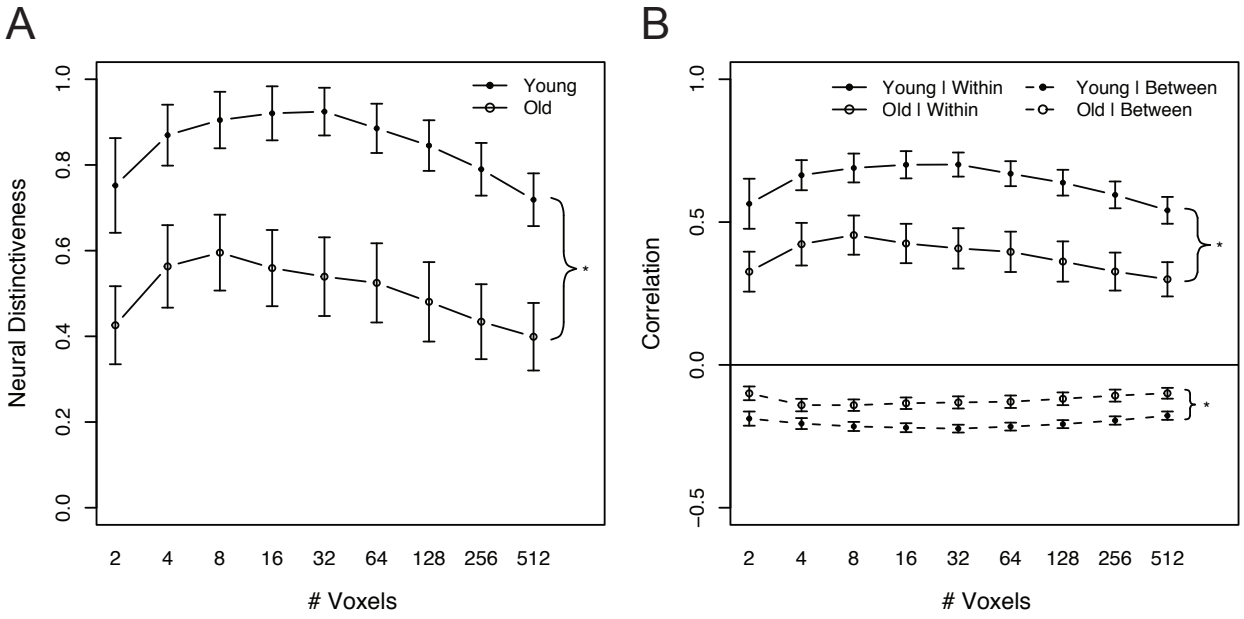
Neural distinctiveness scores were analyzed using a mixed ANCOVA with a between-subjects factor of age (young, old) and a within-subjects covariate of mask size (2 to 512 voxels). Mask size was transformed using the logarithm to the base 2. Visual inspection of the data suggested a quadratic relationship between mask size and distinctiveness (Figure 1A); therefore, the second-order effect of mask size was included in the model.

Critically, the distinctiveness of distributed category representations was significantly diminished in older adults ($F(1, 23) = 11.3$, $p = .0027$; Figure 1A). In other words, activation patterns within peak object-sensitive regions of ventral visual cortex discriminated among visual categories less sensitively in older adults than in younger adults. Pairwise t-tests showed that age differences in neural distinctiveness were significant at each mask size ($t$s(23) >= 2.26, $p$s <= .034).

Neural distinctiveness scores also showed a strong quadratic main effect of mask size: VVC activation patterns for different stimuli were more distinctive at moderate mask sizes and less distinctive at very small and very large mask sizes ($F(1, 23) = 18.7$, $p < .001$; Figure 1A). Distinctiveness is likely relatively low at small mask sizes because patterns across small numbers of voxels are too variable to reliably distinguish among stimuli. On the other hand, distinctiveness scores decrease at large mask sizes because large masks include many voxels that are uninformative about stimulus conditions. Thus, neural distinctiveness is maximized at intermediate mask sizes.

Because the index of neural distinctiveness used here combines information from correlations within and between stimulus categories, age differences in distinctiveness could be driven by differences in within-category correlations, between-category correlations, or both. Thus, we examined the effects of aging on within- and between-category correlations separately. Correlation values were submitted to a mixed ANCOVA including factors of age group, log-transformed mask size, and the square of transformed mask size, as described above.

Both within- and between-category correlations showed robust effects of age group (Figure 1B). Within-category correlations were reduced in older adults ($F(1, 23) = 11.1$, $p = .0029$). In contrast, older adults showed increased (i.e. less negative) correlations between categories ($F(1, 23) = 12.0$, $p = .0021$). Thus, age differences in neural distinctiveness stem from both decreased within-category reliability and increased between-category similarity in older adults[1].




[1] Following the recommendation of an anonymous reviewer, we repeated this analysis after randomly permuting category labels for each run and each subject. In this analysis, we found no difference between age groups. Thus, age differences in neural distinctiveness are specific to non-arbitrary category labels.

**Figure 1. Region-of-interest analysis of age differences in the distinctiveness of neural activation patterns in ventral visual cortex.**
Panel A: Older adults showed significantly lower neural distinctiveness than younger adults. Panel B: Older adults showed significantly lower within-category correlations (solid lines) and significantly higher between-category correlations (dotted lines) than younger adults. Error bars denote the standard error of the mean. Asterisks indicate significant effects of age group.

The preceding analysis focused on patterns of activation within regions of VVC that responded strongly to all object categories. Haxby and colleagues (2001) showed that regions of VVC that activate preferentially to one stimulus category (e.g. faces) can also decode responses to other categories (e.g. houses). Thus, we also examined age differences in neural distinctiveness within regions of VVC that responded maximally to each stimulus category. For each of the four stimulus categories, we identified the voxels within the VVC that showed the strongest response to that category, compared to scrambled images. Neural distinctiveness was significantly reduced in older adults across the voxels most sensitive to faces ($F(1, 23) = 15.0$, $p < .001$), houses ($F(1, 23) = 14.6$, $p < .001$), pseudo-words ($F(1, 23) = 12.5$, $p = .0017$), and chairs ($F(1, 23) = 7.1$, $p = .014$). Finally, age differences in neural distinctiveness persisted when the entire anatomical VVC ROI was considered ($t(23) = 3.23$, $p = .0037$). In sum, age differences in neural distinctiveness are robust across a wide range of voxel selection methods.

Computational accounts of cognitive aging suggest that neural representations of stimuli may be relatively sparse in younger adults and relatively distributed in older adults. In other words, older adults may use may use more neural resources to encode a particular stimulus than younger adults (Li et al., 2001; see Li and Sikström, 2002, Figure 2). Thus, older adults may be able to compensate for increased neural noise by distributing stimulus representations across more processing nodes. If this is the case, age differences in category distinctiveness should be largest for small masks (at which MVPA is most sensitive to sparse representations) and should diminish for larger masks (at which MVPA is sensitive to both sparse and distributed representations). In contrast to this prediction, age differences in neural distinctiveness within the VVC did not vary

with mask size. Interactions between age and the quadratic effect of mask size failed to approach significance ($F < 1$; Figure 1). Similarly, age differences in within- and between-category correlations did not interact with mask size ($F$s < 1). Thus, we found no evidence that older adults can increase the distinctiveness of neural representations by distributing category representations across larger numbers of voxels within the VVC.

Prior studies have reported increased inter-trial variability of the hemodynamic response function in older adults (D'Esposito et al., 1999; Huettel et al., 2001). This variability has been hypothesized to reflect age differences in neuro-vascular coupling (D'Esposito et al., 2003). In other words, increased variability of the BOLD signal in older adults may stem from vascular rather than neural changes. Such non-neural changes in BOLD variability could have biased our results: perhaps age differences in neural distinctiveness are driven solely by age differences in trial-by-trial variability of neuro-vascular coupling. To investigate this possibility, we measured BOLD variability in each subject. We quantified BOLD variability as the average mean-square error (derived from the General Linear Model, implemented in SPM5) within a control brain region not activated by our task, the posterior cingulate cortex (results for this analysis were qualitatively similar when BOLD variance was measured in the VVC instead). We then repeated the analyses described above while statistically controlling for individual differences in BOLD variability. Regardless of the criteria used to define regions of interest within the VVC, age differences in neural distinctiveness remained significant after controlling for BOLD variability (all categories vs. baseline: $F(1, 22) = 8.50$, $p = .008$; faces vs. baseline: $F(1, 22) = 11.79$; $p < .0024$; houses vs. baseline: $F(1, 22) = 11.40$, $p < .0027$; pseudo-words vs. baseline: $F(1, 22) = 9.52$, $p < .0054$; chairs vs. baseline: $F(1, 22) = 4.72$, $p = .041$). High BOLD variability was also associated with reduced neural distinctiveness ($F$s(1, 22) >= 9.28, $p$s <= .006). In summary, both age and BOLD variability had significant effects on neural distinctiveness. Critically, effects of age on distinctiveness survived correction for BOLD variability, suggesting that the age differences reported above cannot be explained solely by differences in neuro-vascular coupling.

## Searchlight analysis

Whole-brain analysis confirmed age differences in neural distinctiveness within the ventral visual pathway: younger adults showed higher category selectivity than older adults in bilateral VVC (Figure 2A; Table 1). Age differences in category distinctiveness were not restricted to the ventral visual stream. Older adults also showed decreased distinctiveness in early visual cortex, including right striate cortex and extending into extrastriate cortex (Figure 2B; Table 1). We also observed age differences beyond the visual cortex. Older adults showed decreased selectivity of category coding in bilateral inferior parietal cortex (Figure 2C; Table 1) and in left and medial prefrontal regions (Figure 2A, 2B; Table 1)[2]. Overall, neural distinctiveness was highest in visual areas (particularly the VVC); distinctiveness scores were reduced in parietal and frontal regions (Table 1).

Prior reports have suggested that older adults are able to compensate for impaired processing in visual cortex using frontal and parietal mechanisms (Park and Reuter-Lorenz, 2009). If frontal circuits can indeed counteract age-related changes in visual processing, then older adults should exhibit higher neural distinctiveness than younger adults in some brain regions outside the visual cortex. However, our data did not support this proposition: no regions showed higher distinctiveness for older adults than younger adults.

[2] Analysis of ventral visual responses showed that age differences in neural distinctiveness did not vary with the number of voxels included in the analysis, suggesting that older adults did not increase the distinctiveness of neural representations by recruiting additional neural resources (see Region-of-interest analysis, above). When we repeated this analysis using the parietal and frontal regions identified by the multivariate searchlight analysis, we found an analogous result: age differences in neural distinctiveness did not decrease as more voxels were included in the analysis.

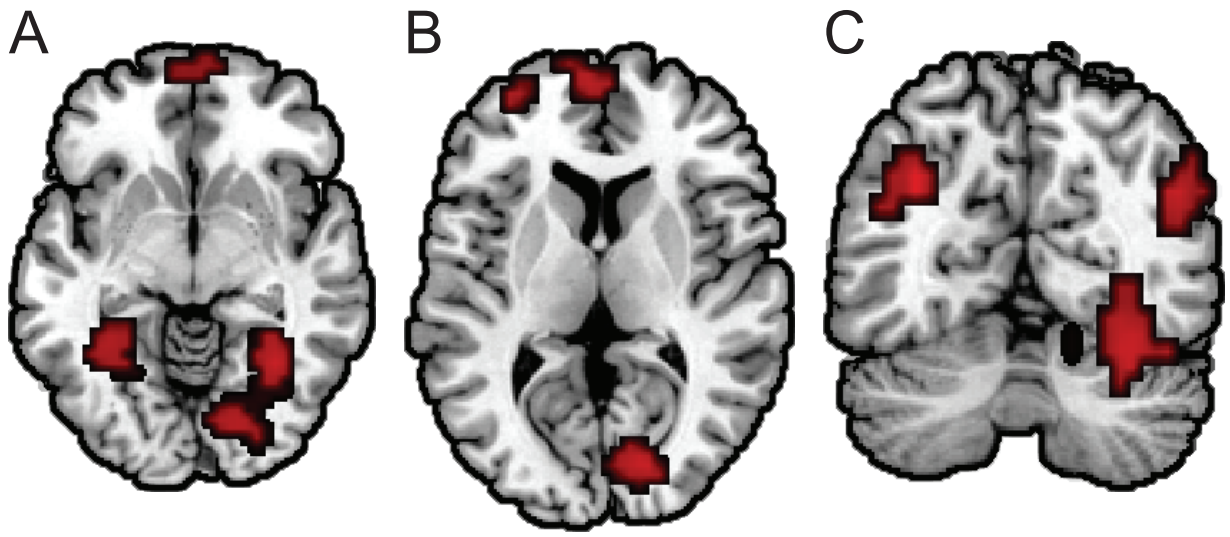



**Figure 2. Whole-brain searchlight analysis of age differences in neural distinctiveness.**
Regions showing significantly higher neural distinctiveness scores for younger compared to older adults are highlighted in red and include bilateral ventral visual cortex (Panel A; z = -6), right striate and left and medial prefrontal cortex (Panel B; z = 8), and bilateral inferior parietal cortex (Panel C; y = -64). No regions showed significantly higher distinctiveness scores for older adults. All coordinates are given in MNI space.

Searchlight analysis revealed age-related decline in neural distinctiveness in several distinct brain regions. Age differences in these regions may stem from a common cause; alternatively, different mechanisms may explain age changes in different regions. To explore these possibilities, we assessed correlations in neural distinctiveness among the brain regions showing an overall age difference in distinctiveness. For each subject, we assessed average neural distinctiveness within four groups of brain regions: early visual (right striate cortex), late visual (bilateral VVC), parietal (bilateral inferior parietal), and prefrontal (medial and lateral PFC). Neural distinctiveness scores were averaged for each subject within 10 mm of the peak activation for each ROI (peak coordinates are reported above). Scatter-plots for all pairs of ROIs are displayed in Figure 3; correlation coefficients are presented in Tables 2 and 3. Correlations were estimated separately for younger and older adults. In younger adults, neural distinctiveness in early and late visual regions was significantly correlated ($r(11) = .84$, $p < .001$). No other correlations were significant ($ps > .05$). Similarly, distinctiveness in early and late visual areas was also significantly correlated in older adults ($r(10) = .86$, $p < .001$). Older adults also

showed significant correlations in distinctiveness between early visual and parietal ROIs ($r(10) = .80$, $p = .0016$) and between late visual and parietal ROIs ($r(10) = .87$, $p = .0016$). No other correlations were significant among the older adults. In sum, neural distinctiveness in early and late visual areas was highly correlated for both younger and older adults. Correlations between other pairs of regions were not significant or were inconsistent across age groups.

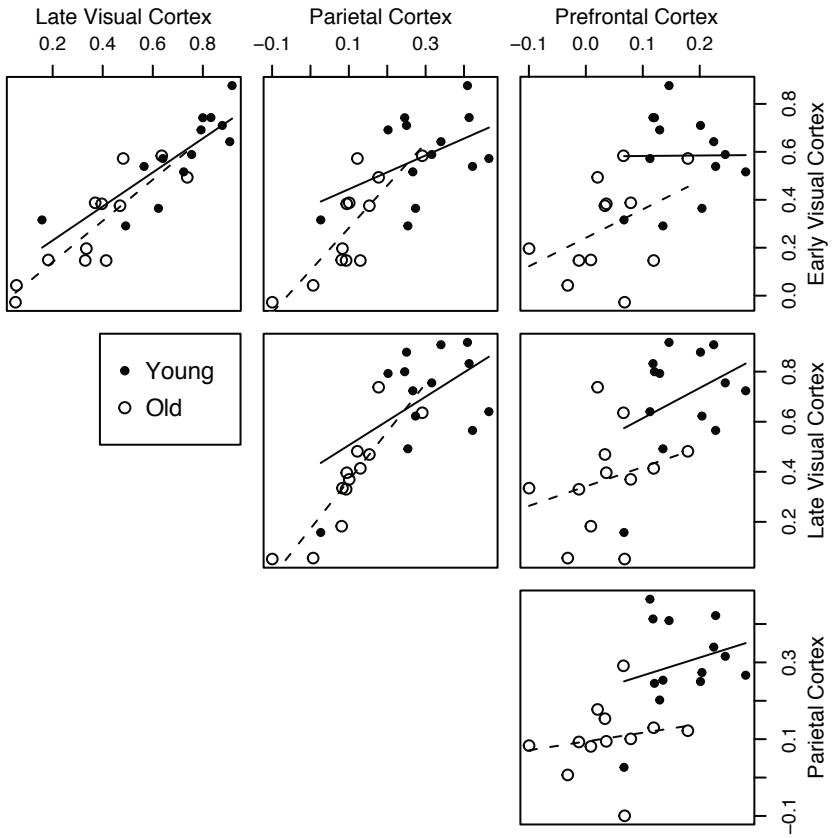



**Figure 3. Correlations of neural distinctiveness scores across regions.** Correlations between right striate and bilateral ventral visual regions were significant in both younger adults (filled circles; solid lines) and in older adults (open circles; dotted lines). Correlation coefficients are provided in Tables 2 and 3.

## Global correlation analysis

Region-of-interest and searchlight analyses focused on local differences in neural distinctiveness. However, aging may also affect the global distribution of category

distinctiveness across the brain. We assessed age differences in the spatial distribution of category coding using a global correlation analysis, including all voxels in the brain.

Results from this global correlation analysis are presented in Figure 4. Each point in this scatter-plot describes the neural distinctiveness in the local neighborhood of a single voxel for younger adults (horizontal axis) versus older adults (vertical axis). This analysis revealed a highly significant linear relationship between age groups ($r = .929$, $p < .001$; Figure 4): voxels with high distinctiveness among younger participants tended to show high distinctiveness in older participants as well. Thus, the neural substrates of category representation were highly similar across age groups. Importantly, however, the slope of the best-fit line was significantly less than one (99.9% confidence interval of $\beta$: .515 to .523; Figure 3). Thus, any given voxel showed nearly double the distinctiveness in younger adults as in older adults. In sum, older adults encoded object category using the same neural resources but with uniformly lower distinctiveness than their younger counterparts.

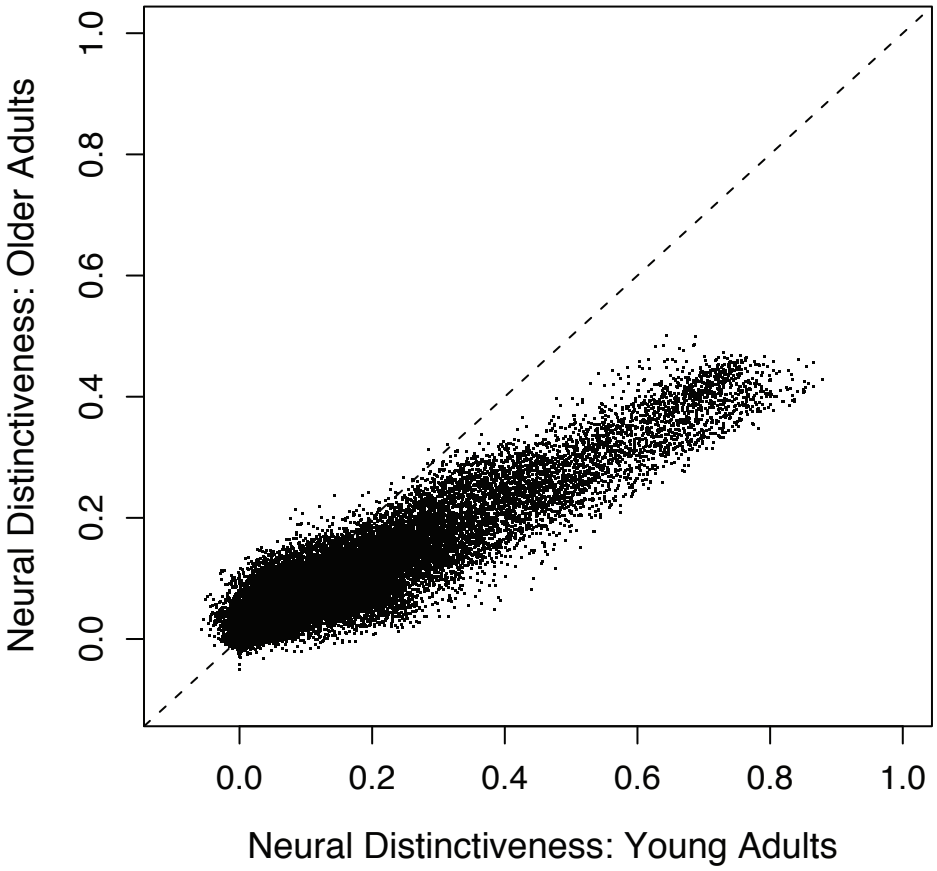



**Figure 4. Global correlation between neural distinctiveness scores in younger and older adults.**
Each point describes the neural distinctiveness in the local neighborhood of a single voxel among younger adults (horizontal axis) and older adults (vertical axis). Both groups used the same neural resources to represent visual stimuli ($r = .929$), but the distinctiveness of any given voxel in older adults was reduced by almost 50% compared to younger adults ($\beta = .519$).

## *Discussion*

Computational models of cognitive aging posit that neural representations become less distinctive in old age (Li et al., 2001). The present study explored age differences in the distinctiveness of distributed visual representations, applying multi-voxel pattern analysis (MVPA) to an earlier study of the aging visual system (Park et al., 2004). In agreement with univariate studies of the aging visual system, we showed that multi-voxel activation patterns in the ventral visual cortex (VVC) evoked by different stimulus

categories were less distinctive among older adults. Critically, this age-related dedifferentiation was not restricted to the VVC; older adults also exhibited decreased neural distinctiveness in early visual cortex, inferior parietal cortex, and medial and lateral prefrontal cortex. Finally, results from multiple analyses provided no support for the notion that older adults compensate for decreased selectivity in perceptual brain regions by increasing selectivity in other regions.

We first tested the hypothesis that fMRI activation patterns elicited by different stimulus categories would become less distinctive in old age. Multiple analyses confirmed age differences in neural distinctiveness. Region-of-interest analysis using subject-specific anatomical masks of the ventral visual cortex (VVC) showed that activation patterns in object-sensitive regions of VVC are less distinctive among older adults (Figure 1A). These age differences in neural distinctiveness reflected changes in both within- and between-category correlations (Figure 1B). Older adults showed significantly lower correlations within categories across runs. In other words, fine-grained spatial activation patterns for a given category are less consistent across time in old age. Furthermore, older adults showed significantly higher (i.e. less negative) correlations between categories. Thus, differences between categories were less pronounced in older adults. Finally, we showed that age differences in neural distinctiveness were not specific to a particular choice of ROI within the VVC: distinctiveness was uniformly and significantly reduced in older adults across all ROIs tested, including the entire anatomical ROI.

Second, we conducted a whole-brain analysis of age differences in neural distinctiveness. A multivariate searchlight procedure (Kriegeskorte et al., 2006) confirmed age-related differences in the ventral visual stream (Figure 2A). This analysis also revealed age differences in early visual cortex and inferior parietal cortex, as well as medial and lateral prefrontal regions (Figure 2B, 2C). Critically, no brain regions showed higher distinctiveness in older adults compared to younger adults. Correlations among regions revealed strong relationships between neural distinctiveness scores in early and late visual regions in both age groups. On the other hand, distinctiveness

scores in visual regions were uncorrelated with scores in frontal regions (Figure 3; Tables 1 and 2). These results suggest that a common mechanism may explain age-related declines in both early and late visual areas, while an independent mechanism may explain declines in frontal regions. Impaired coding of simple visual features like orientation and spatial frequency in early visual cortex may impact the coding of object category in the VVC. Consistent with this speculation, single-unit recording studies of visual representation indeed show that visual features are encoded less selectively in V1 and V2 in senescent macaques (Schmolesky et al., 2000; Wang et al., 2005). Alternatively, correlations between early and late visual areas may reflect a general disruption of visual attention in older adults (Madden, 2007). Finally, we assessed the ability of older adults to compensate for reduced neural distinctiveness in visual cortex by increasing selectivity in other brain regions. Prior studies suggest that older adults may compensate for altered visual processing by engaging additional neural circuits (Grady et al., 1994; Madden et al., 2004). In contrast to this view, our results suggest that older adults do not compensate for decreased neural distinctiveness in the visual cortex by increasing distinctiveness in other regions. First, age differences in distributed category coding did not vary with the number of voxels analyzed, suggesting that older adults did not compensate for noisy ventral visual responses by engaging more processing nodes within the VVC (Figure 1). Second, neural distinctiveness scores were higher for younger adults than for older adults across several brain regions (Figure 2), but no regions showed higher distinctiveness for older adults than for younger adults. Finally, a global correlation analysis revealed that aging affects the distinctiveness but not the spatial distribution of category coding. In other words, older and younger adults use the same brain regions to encode visual categories, but neural distinctiveness is uniformly decreased by about 50% throughout the aging brain (Figure 4). In sum, we found no evidence that older adults can increase the distinctiveness of visual representations by engaging additional processing resources within the VVC, by recruiting brain regions outside the visual cortex, or by altering the spatial distribution of category coding across the brain.

Our results are broadly consistent with studies of the aging visual system in non-human animals. Leventhal and colleagues (Leventhal et al., 2003; Schmolesky et al., 2000) found that single neurons in early visual cortex showed weaker stimulus preferences in senescent macaques compared to young controls. Similar results have been reported in cats (Hua et al., 2006) and rats (Wang et al., 2006). In other words, single-cell responses to different visual stimuli are more similar in older animals. The present study confirms and extends these results. We report an analogous effect in humans: our results show that responses to different visual stimuli are less distinctive in older adults than in younger adults. Furthermore, while single-cell studies of the aging visual system have focused on local changes in visual activity, our results reveal age differences in distributed representations as well.

While animal studies have focused on age differences in visual responses in early visual (Schmolesky et al., 2000) and dorsal-stream regions (Yang et al., 2008), we report age differences in category representation in the ventral visual cortex. However, our observation of age-related deficits in early visual cortex suggests that age differences in ventral visual activity may stem from altered processing of simple features in primary visual cortex. Indeed, we found that neural distinctiveness scores in early visual cortex were strongly predictive of distinctiveness in the ventral visual cortex. Aging is also associated with impaired communication within the visual cortex (Wang et al., 2005), providing further support for the notion that the ventral visual stream receives degraded inputs from early visual cortex in aging humans. The present study does not directly test this hypothesis; future research should continue to investigate the relationship between age-related changes in early and late visual processing.

Our results also dovetail with research on aging and neural complexity. According to Tononi and colleagues (1998; 1994), complex neural systems are characterized by both functional integration and functional segregation. Our findings of reduced within-category correlations in older adults may reflect declines in functional integration within neural networks that process visual objects; on the other hand, enhanced between-

category correlations in older adults may reflect impaired functional segregation. Thus, our results are compatible with the view that neural complexity is reduced in older adults. In this regard, our findings agree with computational modeling work by Li and Sikström (2002), who linked age-related declines in neural distinctiveness to reduced computational complexity. Future studies should use explicit measures of neural complexity (Tononi et al., 1994) to assess age differences in functional integration and segregation in visual cortex.

Future studies should also test the generality of our results across different tasks and experimental designs. Participants did not make overt responses in the present study; our results do not exclude the possibility that older adults can compensate for reduced neural distinctiveness in the context of a task that requires them to respond to visual stimuli. Future studies should measure age differences in neural distinctiveness in the context of a demanding task and relate distinctiveness measures to behavioral indices of compensation. Forthcoming work from our lab shows that neural distinctiveness is indeed associated with a range of behavioral tests in older adults (Park et al., unpublished data). The present study also used a block design, which does not permit analysis of individual trials or different stages within a trial. Future studies should extend this work to event-related designs to reveal the temporal evolution of age differences in neural distinctiveness.

Previous research has documented age-related increases in the variability of the hemodynamic response function across trials in early vision and motor regions (D'Esposito et al., 1999; Huettel et al., 2001). To the extent that these increases in response variability are attributable to non-neural processes (e.g. altered neuro-vascular coupling), they might artificially depress measures of neural distinctiveness in older adults. As recommended by D'Esposito and colleagues (2003), we took several steps to minimize the effects of age differences in BOLD variability on our results. First, our analysis focused on interactions between age group and experimental conditions, avoiding confounds due to age differences in overall response magnitude. Second, we

used $\beta$ values and not the usual *t*-statistic to assess responses to experimental stimuli; because $\beta$ values are not scaled by model error, they may be less susceptible to individual differences in BOLD variability (Rypma and D'Esposito, 2000). Third, reasoning that averaging across time would reduce signal variability, we averaged BOLD responses both (1) across trials within a block and (2) across blocks within a run before submitting data to MVPA.

In addition to these methodological precautions, several features of our data also suggest that the age differences we report here cannot be explained solely in terms of non-neural age differences. First, in a previous report of these data, we found that average *t*-values in the VVC did not differ significantly between age groups (Park et al., 2004). In fact, *t*-values were non-significantly higher in older adults. This observation argues against an age difference in signal-to-noise ratio (SNR) in our data: if older adults have reduced SNR, they should also have lower *t*-values. However, this is not the case in this analysis. Second, in the present report, we showed that age differences in neural distinctiveness remained significant after statistically controlling for individual differences in BOLD variability.

Age differences in neuro-vascular coupling may also have influenced our analysis of inter-regional correlations in neural distinctiveness (Figure 3). Specifically, positive correlations in distinctiveness scores between brain regions may reflect global changes in BOLD variability (D'Esposito et al., 2003). However, two features of our data are inconsistent with this view. First, correlations between posterior and anterior regions were generally small and non-significant (Tables 2 and 3), arguing against a global explanation of individual differences in distinctiveness. Second, if correlations were driven by age differences in neuro-vascular coupling, then these correlations should vanish when only considering younger participants, who were assumed to have healthy vascular function. However, we found significant positive correlations between regions within younger adults as well as older adults.

In summary, while age groups may differ in both neural and non-neural components of the BOLD signal, we argue that non-neural differences cannot adequately explain our finding of reduced neural distinctiveness in older adults. Future studies should continue to investigate the relationship between BOLD response properties and MVPA, and should replicate the present results using non-hemodynamic measurements like EEG and MEG.

In conclusion, we show for the first time that the distinctiveness of distributed patterns of neural activation declines in old age. We observed age differences in neural distinctiveness in early and late visual cortex, as well as in parietal and prefrontal regions. Moreover, our results provided no support for the notion that older adults can increase the distinctiveness of neural representations. Our results lend novel support to computational models of cognitive aging and have important implications for the understanding of compensatory mechanisms in older adults. Finally, our results highlight the value of multivariate pattern analysis to the study of representational change in the aging brain.

## Tables

**Table 1.** Age differences in neural distinctiveness.

| Anatomical location | Number of voxels | MNI coordinates | | | Neural distinctiveness | | Peak t-score |
|---|---|---|---|---|---|---|---|
| | | *X* | *Y* | *Z* | Younger adults | Older adults | |
| R. Visual Cortex | 289 | 15 | -79 | 15 | .58 | .23 | 5.20 |
| L. VVC | 40 | -30 | -56 | -10 | .78 | .39 | 3.94 |
| R. VVC | 289 | 34 | -56 | -5 | .74 | .34 | 4.54 |
| R. Inferior Parietal Cortex | 66 | -34 | -60 | 35 | .34 | .11 | 5.70 |
| L. Inferior Parietal Cortex | 32 | 49 | -64 | 30 | .30 | .05 | 4.41 |
| L. Prefrontal Cortex | 136 | -30 | 53 | 10 | .19 | .03 | 4.09 |
| M. Prefrontal Cortex | 136 | -11 | 53 | 30 | .25 | .05 | 5.39 |

**Table 2**. Correlations between neural distinctiveness scores across ROIs. Younger adults only.

| | Early visual | Late visual | Parietal | Prefrontal |
|---|---|---|---|---|
| Early visual | . | ***r* = .84*** <br> ***p* < .001** | *r* = .46 <br> *p* = .11 | *r* = .007 <br> *p* = .98 |
| Late visual | . | . | *r* = .54 <br> *p* = .058 | *r* = .37 <br> *p* = .22 |
| Parietal | . | . | . | *r* = .26 <br> *p* = .40 |
| Prefrontal | . | . | . | . |

**Table 3**. Correlations between neural distinctiveness scores across ROIs. Older adults only.

| | Early visual | Late visual | Parietal | Prefrontal |
|---|---|---|---|---|
| Early visual | . | ***r* = .86*** <br> ***p* < .001** | ***r* = .80*** <br> ***p* = .0016** | *r* = .42 <br> *p* = .18 |
| Late visual | . | . | ***r* = .87*** <br> ***p* < .001** | *r* = .27 <br> *p* = .39 |
| Parietal | . | . | . | *r* = .18 <br> *p* = .58 |
| Prefrontal | . | . | . | . |

# Chapter 3: Age-related neural dedifferentiation in the motor system

## *Introduction*

The dedifferentiation hypothesis of aging argues that different mental operations increasingly rely on shared neural substrates in old age (Li et al., 2001; Park et al., 2004). Consistent with this view, recent studies suggest that neural representations of visual stimuli become less distinctive with increasing age. Psychophysical studies show that aging impairs perception of moving images (Bennett et al., 2007), contours (Roudaia et al., 2008), and object stimuli (Owsley et al., 1981). In addition, single-neuron recording studies show that visual neurons are tuned to stimulus features less selectively in older macaques than in young controls (Leventhal et al., 2003; Schmolesky et al., 2000). Neuroimaging studies of aging humans offer the strongest evidence for this view. Brain regions that are specialized for specific categories of visual stimuli in young adults become less selective in old age (Grady et al., 1994; Park et al., 2004). Furthermore, neural adaptation to face stimuli increases with age, suggesting that the aging brain is less able to differentiate one face from another (Goh et al., 2010). Finally, distributed patterns of brain activation evoked by different visual stimuli are less distinctive in older adults than in young adults (Carp et al., 2010a; Carp et al., 2011; Park et al., 2010).

Although several studies have investigated age-related dedifferentiation of visual processing, less is known about the relationship between age and the neural representation of movement. Aging is associated with impaired motor performance across a range of tasks and ability domains (Seidler et al., 2010), suggesting that movement representations may be disrupted in old age. Consistent with this view, older

adults show stronger activation than young adults in ipsilateral motor cortex during unimanual movement (Mattay et al., 2002; Ward and Frackowiak, 2003). Older adults also show increased motor-related activation in sensory and executive regions, relative to young adults (Heuninckx et al., 2005; Heuninckx et al., 2008). Finally, motor cortical representations increase in spatial extent with age (Bernard and Seidler, 2011). These results may reflect decreased distinctiveness of motor representations in old age. Alternatively, however, they may indicate compensation for age-related declines in cognitive or sensory function (Heuninckx et al., 2008; Park and Reuter-Lorenz, 2009).

Thus, the present study investigated the effects of aging on the neural representation of movement. Previous studies of the aging motor control system have focused on univariate measures, which may not capture fine-grained spatial information patterns that discriminate between task conditions. Thus, we assessed the distinctiveness of motor representations in young and older adults using multi-voxel pattern analysis (MVPA), which is more sensitive to such patterns (Haynes and Rees, 2006). According to the dedifferentiation hypothesis, the neural representations of different motor states should be less distinctive in older adults than in young adults (Li et al., 2001). We define the representation of a particular motor state as the distributed pattern of neural activation evoked by that state (Li and Sikström, 2002); the representations of two motor states are distinctive to the extent that one pattern can be distinguished from the other. Thus, we predicted that the multi-voxel activation patterns evoked by left- and right-hand finger tapping would be less distinctive in older adults, relative to young adults.

## *Methods*

### Ethics statement

All study procedures were reviewed and approved by the University of Illinois Institutional Review Board, and all participants provided detailed written consent before their involvement in this study according to the principles of the Declaration of Helsinki.

## Participants

Twenty-four older adults and twenty-three young adults participated in the experiment. Data from five older adults and four young adults were discarded due to excessive head motion, improper head coil placement, vision problems, or failure to follow instructions, leaving data from eighteen older adults (mean age: 64.67; standard deviation: 2.9; range: 60-69; nine female) and nineteen young adults (mean age: 22.2; standard deviation: 2.7; range: 18-29; 9 female) for analysis. All participants were right-handed native English speakers; participants were not taking medications with psychotropic or vascular effects, and were free of MRI safety contraindications. All participants scored at least 26 on the mini-mental state exam (Folstein et al., 1975).

## Experimental design

Participants performed simple motor and visual tasks while fMRI data were collected. The motor task comprised two six-minute runs. In each block, subjects were instructed to tap their left index finger (three blocks per run), right index finger (three blocks per run), or to alternate between left and right index fingers (six blocks per run). Large red arrows were used to cue each condition. Participants tapped in time with a loud 1 Hz metronomic tick presented through the scanner intercom. Blocks were presented in one of two possible fixed orders, either (1) left finger, alternate, right finger, alternate, etc., or (2) right finger, alternate, left finger, alternate, etc.; block orders were counterbalanced across runs and subjects. Each block lasted for 30 seconds; there was no gap between blocks. An independent analysis of the visual task, which does not overlap with the present study, has been published in a separate report (Park et al., 2010).

Stimuli were presented using E-prime (Psychology Software Tools, Pittsburgh, PA) and displayed using a back-projection system. Responses were recorded using a Lumina response pad (Cedrus Corporation, San Pedro, CA).

## Data acquisition

Brain images were acquired using a 3T Allegra head-only MRI scanner (Siemens, Erlangen, Germany). Blood oxygen level dependent (BOLD) images were acquired using an echo planar imaging sequence (TR=2000 ms, TE=25 ms, FA=80°, FOV=220 mm). Each volume included 36 axial slices collected parallel to the AC-PC line. Each slice was 4.4 mm thick, with an in-plane resolution of 3.44 by 3.44 mm. A high resolution (1 mm isotropic voxels) T1-weighted MPRAGE image was also collected for subsequent normalization to standard space.

## Pre-processing

Data were pre-processed using SPM8 software (Wellcome Department of Cognitive Neurology, London, UK) running under Matlab R2011b (The Mathworks, Inc., Natick, MA, USA). Functional images were corrected for slice timing, realigned to the first functional volume, and coregistered to the high-resolution structural image. Spatial normalization and smoothing may distort or remove fine-grained information from multivariate analysis (Haynes and Rees, 2006). Thus, neither normalization nor smoothing was applied before multivariate analysis.

## Model estimation

Neural responses were estimated using the General Linear Model, implemented in SPM8. Responses to the left- and right-hand tapping conditions were modeled using a

block design; the alternation condition was not explicitly modeled but was treated as an implicit baseline. Model estimation included twenty-four head motion regressors as nuisance covariates, including the linear, squared, time-shifted, and squared time-shifted transformations of the six rigid-body movement parameters.

## Multi-voxel pattern analysis

Next, we used the activation estimates from the univariate analysis described above to assess the distinctiveness of multi-voxel representations of left- and right-hand tapping. As described by Haxby and colleagues (2001), neural distinctiveness was defined as the difference between pattern similarity within and between conditions. Specifically, the distinctiveness between conditions for a given set of voxels was defined as the difference between the mean Fisher-transformed Pearson correlations across those voxels' activation values within and between the two conditions (Haushofer et al., 2008; Haxby et al., 2001). Positive distinctiveness scores (i.e., greater within-condition than between-condition similarity) indicate that multi-voxel activation patterns distinguished between conditions; distinctiveness scores of zero indicate that activation patterns were similar across conditions. We chose this approach over alternative classification methods, such as support vector machines and artificial neural networks, because of its computational simplicity and to avoid ceiling effects in classifier accuracy.

To generate whole-brain maps of pattern distinctiveness, we combined the correlation analysis described above with a multivariate searchlight procedure (Kriegeskorte et al., 2006). For each voxel in the brain, we identified all voxels within a 12-mm-radius sphere centered on that voxel. Next, we estimated the distinctiveness between conditions across this group of voxels. The resulting distinctiveness score was then entered as the value for the center voxel. This procedure was repeated for each voxel in the brain, yielding a whole-brain map of distinctiveness between conditions. Neural distinctiveness

maps were subsequently normalized into Montreal Neurological Institute (MNI) space for further analysis.

### Voxel-based morphometry

Gray matter volume declines with increasing age in regions associated with motor control, including the cerebellum and caudate (Raz et al., 2005). Recent research shows that these age-related changes in brain structure may explain age differences in brain function (Kalpouzos et al., 2011). Thus, the present study also investigated whether age differences in the distinctiveness of motor representations could be explained by differences in gray matter volume. Voxel-based morphometry (VBM) was implemented using the VBM8 toolbox for SPM8 (http://dbm.neuro.uni-jena.de/vbm.html). High-resolution anatomical images were segmented, modulated using the non-linear warping parameters from the normalization results, and smoothed with a Gaussian kernel of 8 mm full width at half maximum.

## *Results*

First, we identified the brain regions in which multi-voxel patterns distinguished between left- and right-hand finger tapping conditions using a whole-brain searchlight procedure, collapsing across age groups. This analysis used a height threshold of $p \leq 1e\text{-}7$ and an extent threshold of $k \geq 50$ voxels. Results indicated that distributed patterns of activation in bilateral primary motor cortex (M1), supplementary motor cortex (SMA), and medial and lateral cerebellum distinguished between conditions (Table 4, Figure 5).

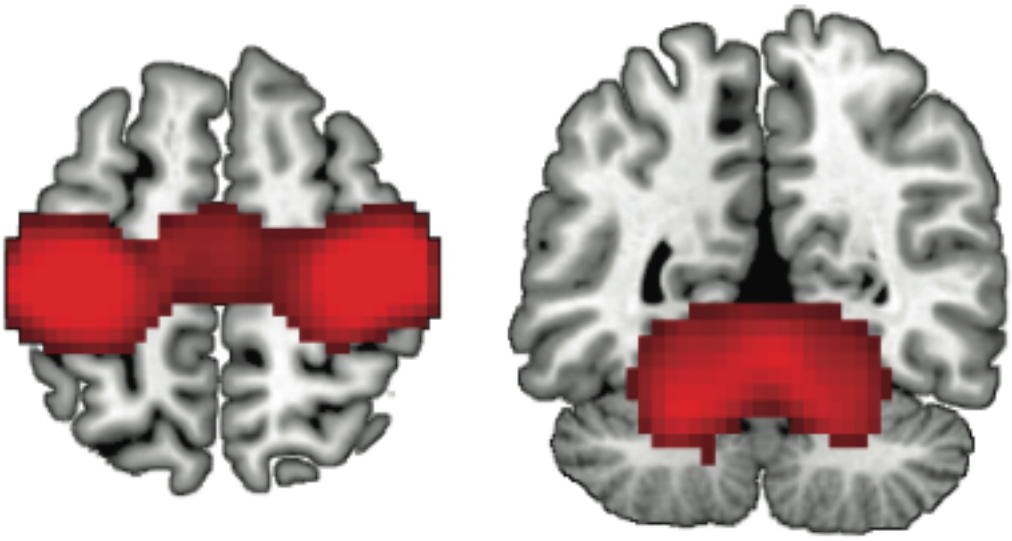


**Figure 5. Whole-brain searchlight analysis of the distinctiveness of motor representations, collapsing across age.**
Distributed patterns of activation in primary motor cortex, pre-supplementary motor area (left panel; z = 56) cerebellum (right panel; y = -52) reliably distinguished between left- and right-hand finger tapping. Coordinates are reported in MNI space.

Next, we compared neural distinctiveness across age groups in each region highlighted by the preceding searchlight analysis. Regions of interest were defined as spheres of 6 mm in radius centered on the local maxima of the searchlight map. In each region, the distinctiveness of activation patterns evoked by left- and right-hand tapping was significantly lower in older adults than in young adults (Figure 6; left M1: $t(35) = 3.79$, $p < 0.001$; right M1: $t(35) = 3.41$; $p = 0.0016$; SMA: $t(35) = 4.08$, $p < 0.001$; left cerebellum: $t(35) = 3.36$; $p = 0.0019$; right cerebellum: $t(35) = 4.13$, $p < 0.001$; medial cerebellum: $t(35) = 3.57$, $p = 0.0011$). Age differences in neural distinctiveness were driven by changes in both within- and between-condition similarity: older adults showed decreased within-category similarity (Figure 7, left panel; left M1: $t(35) = 2.97$, $p = 0.0053$; right M1: $t(35) = 2.71$, $p = 0.010$; SMA: $t(35) = 3.32$, $p = 0.0021$; left cerebellum:

$t(35) = 2.15$, $p = 0.038$; right cerebellum: $t(35) = 3.20$, $p = 0.0029$; medial cerebellum: $t(35) = 2.75$, $p = 0.0093$) and increased between-category similarity (Figure 7, right panel; left M1: $t(35) = 3.32$, $p = 0.0021$; right M1: $t(35) = 2.64$, $p = 0.012$; SMA: $t(35) = 2.35$, $p = 0.025$; left cerebellum: $t(35) = 3.14$, $p = 0.0034$; right cerebellum: $t(35) = 3.32$, $p = 0.0021$; medial cerebellum: $t(35) = 3.11$, $p = 0.0037$) in all regions of interest.

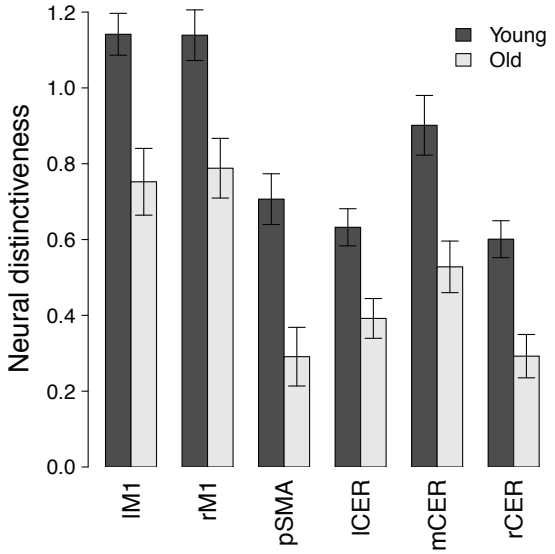



**Figure 6. Region-of-interest analysis of neural distinctiveness in the motor network.**
Neural distinctiveness was reduced throughout the motor network in older adults, relative to young adults. Error bars denote the standard error of the mean.

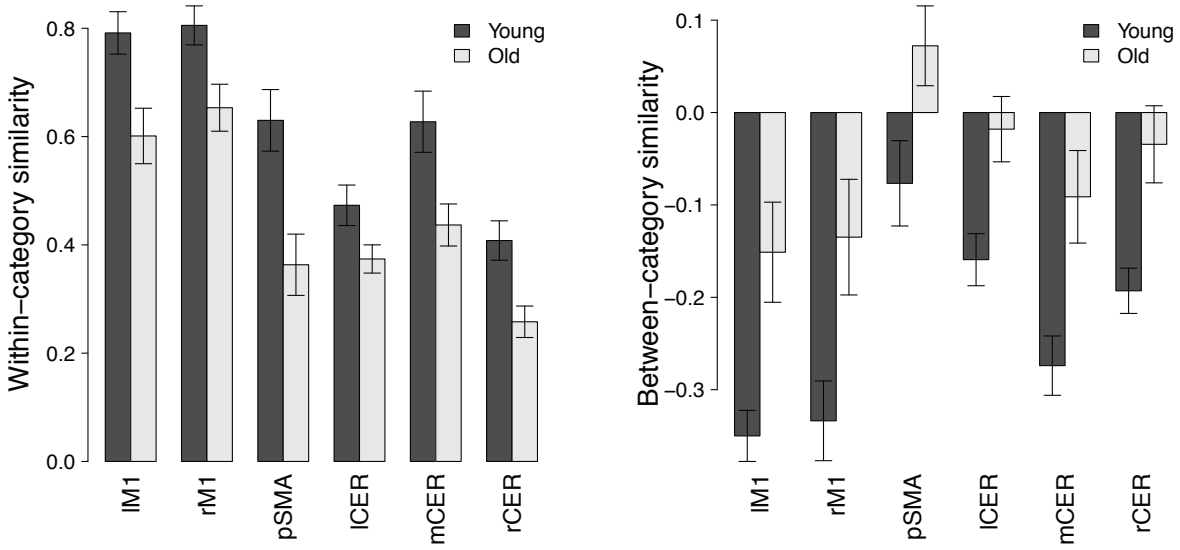



**Figure 7. Region-of-interest analysis of within- and between-category similarity in the motor network.**
Older adults showed reduced within-category similarity (left panel) and increased between-category similarity (right panel) throughout the motor network. Error bars denote the standard error of the mean.

Next, we assessed the contributions of structural changes to the age differences in neural distinctiveness described above using voxel-based morphometry (VBM). In each region of interest, gray matter volume was significantly reduced in older adults, relative to young adults (left M1: $t(35) = 7.81$, $p < 0.001$; right M1: $t(35) = 7.60$, $p < 0.001$; SMA: $t(35) = 6.20$, $p < 0.001$; left cerebellum: $t(35) = 4.74$, $p < 0.001$; right cerebellum: $t(35) = 3.61$, $p < 0.001$; medial cerebellum: $t(35) = 4.15$, $p < 0.001$). However, after controlling for individual differences in gray matter volume, age differences in neural distinctiveness remained highly significant in left primary motor cortex ($t(35) = 2.49$, $p = 0.018$), supplementary motor area ($t(35) = 3.22$, $p = 0.0028$), lateral cerebellum (left: $t(35) = 3.56$, $p = 0.0011$); right: $t(35) = 3.80$, $p < 0.001$), and medial cerebellum ($t(35) = 2.81$, $p = 0.0081$); the age difference in right primary motor cortex was no longer significant ($t(35) = 1.16$, *n.s.*).

Finally, we conducted an exploratory whole-brain analysis of the effects of age group on neural distinctiveness. This analysis used a height threshold of $p \leq 0.005$ and an extent threshold of $k \geq 50$ voxels. Results confirmed that distinctiveness was reduced in older adults throughout the motor execution network. Furthermore, we also observed decreased neural distinctiveness among older adults in bilateral insula (Table 5, Figure 8). No regions showed greater distinctiveness for older adults than for young adults.

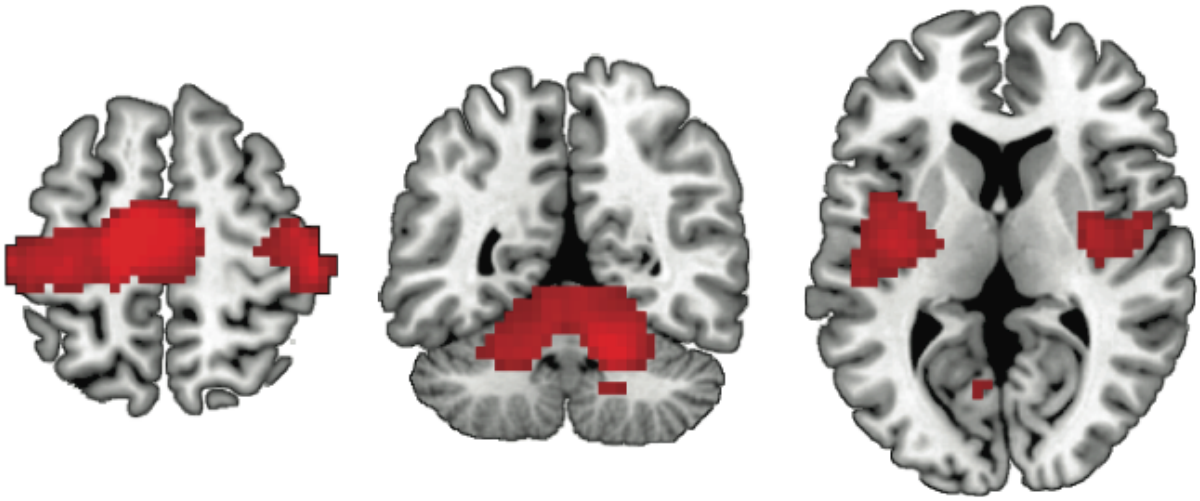


**Figure 8. Whole-brain searchlight analysis of age differences in motor distinctiveness.**
Neural distinctiveness was significantly higher in young adults than in older adults in primary motor cortex, pre-supplementary motor area (left panel; z = 56), cerebellum (center panel; y = -52), and insula (right panel; z = 8). Coordinates are reported in MNI space.

## *Discussion*

The dedifferentiation hypothesis of cognitive aging argues that representations of different mental states become more similar with increasing age (Li et al., 2001). Recent neuroimaging studies of visual perception support this view, indicating that distributed patterns of brain activation evoked by different visual stimuli are less distinctive among older adults than young adults (Carp et al., 2011; Park et al., 2010). A range of motor skills, including movement speed, coordination, and postural stability, decline with increasing age (Seidler et al., 2010). Such findings suggest that the distinctiveness of

motor representations may also decrease in old age. However, studies of the effects of aging on representational distinctiveness have focused on perception; less is known about the relationship between age and motor representations.

The present study used multi-voxel pattern analysis (MVPA) to investigate the effects of age on the distinctiveness of motor representations. We found that motor distinctiveness was reduced among older adults in primary motor cortex, the supplementary motor area, the insula, and the cerebellum. No brain regions showed greater distinctiveness for older adults than young adults, suggesting that older adults do not compensate for decreased motor distinctiveness by extending motor representations to additional brain regions. Thus, previous reports of age-related over-activation during motor performance (Heuninckx et al., 2008; Mattay et al., 2002) may reflect compensation for motor deficits via the recruitment of additional cognitive control resources that do not directly encode motor actions. In other words, although previous studies indicate that older adults can indeed compensate for declining neural function, our results imply that this compensation does not involve the extension of distinctive motor representations to additional regions not recruited by young adults. Finally, although we observed age-related losses of gray matter volume in regions related to motor control, these differences in brain structure did not account for age-related declines in motor distinctiveness.

Our results provide novel support for the dedifferentiation hypothesis. In particular, we found that age-related neural dedifferentiation characterizes the representation of action as well as perception. Recent studies of animals suggest that neural specialization may decline with age in the auditory (Zhou and Merzenich, 2007) and somatosensory domains as well (David-Jürgens et al., 2008); future studies might conduct complementary tests in aging humans. In addition, little is known about the causes of age-related dedifferentiation. Park and colleagues (under review) argue that dedifferentiation in the visual system reflects broadened tuning curves in some brain regions and attenuated activation in others; future research should investigate the

contributions of age-related broadening and attenuation to dedifferentiation of the motor cortex.

Recent studies have also linked dedifferentiation to age differences in neurotransmitter function. For example, Li and colleagues (2001) have hypothesized that dedifferentiation reflects age-related declines in dopamine availability, arguing that decreased dopamine function leads to increased neural noise in old age. Indeed, older adults with greater dopamine transporter binding exhibit faster simple reaction times (van Dyck et al., 2008), and treatment with the dopamine precursor levodopa improves motor performance in the elderly (Floel et al., 2008). Age-related declines in motor representations may also be accelerated in movement disorders like Parkinson's disease (Seidler et al., 2010). In addition, recent studies have linked age differences in GABA-ergic inhibition to declining neural selectivity. In particular, age-related visual impairments are accompanied by selective losses of GABA-reactive neurons in cats (Hua et al., 2008), and increased GABA availability is associated with improved motor control in humans (Boy et al., 2010). Age differences in dopamine, GABA, and other neurotransmitter systems may also exert interactive effects on motor representation and motor performance. Future research should continue to explore the neurochemical origins of age-related dedifferentiation.

The present findings also highlight the complexity of structure-function relationships across the lifespan. Although age-related declines in brain structure integrity explain age differences in activation in certain brain regions during certain tasks (Kalpouzos et al., 2011), the present results show that age differences in the distinctiveness of motor and visual representations are not explained by differences in brain structure. Future research might investigate the contexts in which developmental differences in brain function can, and cannot, be attributed to differences in brain structure.

Although the present study was designed to test theoretical models of cognitive aging, our findings also have important implications for applied research. In particular, our

results suggest that brain-computer interface (BCI) devices may be less effective in older adults than in young adults. These devices often rely on neural signals related to motor execution or imagery, and, as such, require that different motor states correspond to distinctive neural representations. The present finding of reduced motor distinctiveness in older adults thus implies that the performance of BCI systems tested on healthy young adults will likely degrade when used with older patients.

Interpretation of the present results is constrained by a number of limitations that we hope will be addressed in future studies. For example, our sample included young and older adults, but not middle-aged adults. Thus, we cannot yet determine whether age-related changes in motor representations progress gradually over time or onset rapidly in old age. Furthermore, because the present study used a simple unimanual finger tapping task, we were unable to assess the effects of aging on the representation of complex movements. Finally, because we used a block design, we were unable to examine the time-course of neural responses to individual movements. Thus, future studies using middle-aged subjects, more complex movement tasks, and event-related task designs could considerably expand our understanding of age differences in movement representations.

In sum, our findings provide new support for the dedifferentiation hypothesis of aging, showing that neural representations of motor actions grow less distinctive in old age. Further, our findings raise new questions about the generality and causes of age differences in neural representation. Finally, the present study highlights the value of multivariate analytic techniques for the study of group differences in neural representation.

## Tables

**Table 4. Whole-brain searchlight analysis of motor representational distinctiveness, collapsing across age.**

| Brain regions | Number of voxels | MNI coordinates | | | Peak t-score |
|---|---|---|---|---|---|
| | | X | Y | Z | |
| L. motor cortex | 2202 | -43 | -26 | 56 | 18.33 |
| R. motor cortex | 2202 | 43 | -19 | 56 | 18.80 |
| Pre-supplementary motor area | 2202 | 2 | -13 | 60 | 10.13 |
| L. cerebellum | 1207 | -22 | -50 | -28 | 15.04 |
| M. cerebellum | 1207 | 2 | -57 | -15 | 14.23 |
| R. cerebellum | 1207 | 22 | -50 | -28 | 11.33 |

**Table 5. Whole-brain searchlight analysis of age differences in motor distinctiveness.**

| Brain regions | Number of voxels | MNI coordinates | | | Peak t-score |
|---|---|---|---|---|---|
| | | X | Y | Z | |
| L. motor cortex | 967 | -36 | -16 | 60 | 3.85 |
| R. motor cortex | 242 | 50 | -13 | 60 | 4.43 |
| Pre-supplementary motor area | 967 | -15 | -16 | 56 | 6.08 |
| L. cerebellum | 752 | -22 | -50 | -28 | 3.52 |
| M. cerebellum | 752 | -2 | -61 | -6 | 4.21 |
| R. cerebellum | 752 | 19 | -44 | -28 | 4.88 |
| L. insula | 323 | -36 | -9 | 3 | 4.17 |
| R. insula | 176 | 36 | -9 | 12 | 3.56 |

# Chapter 4: Age differences in the neural representation of working memory revealed by multi-voxel pattern analysis.

## *Introduction*

Computational models of cognitive aging posit that neural representations of different mental states become less distinctive in old age (Li et al., 2001), a view referred to as the dedifferentiation hypothesis. Consistent with this notion, behavioral studies show increases in correlations among cognitive and perceptual abilities across the adult lifespan (Baltes and Lindenberger, 1997; Lindenberger and Baltes, 1994). Furthermore, neuroimaging studies show that tasks associated with unilateral brain activation in young adults evoke bilateral activation in older adults (Cabeza et al., 2002; Duverne et al., 2009; Reuter-Lorenz et al., 2000). Similarly, neural specialization in object-sensitive visual cortex decreases in old age (Park et al., 2004). These findings imply that different mental operations increasingly rely on shared neural substrates in the aging brain.

However, age differences in the distinctiveness of neural representations may not be uniform across experimental conditions. In particular, the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model predicts that age differences in neural engagement should vary with the level of task demand (Reuter-Lorenz and Cappell, 2008). According to CRUNCH, declining neural efficiency leads older adults to recruit more neural resources than young adults at low levels of task demand. However, as task demands increase, older adults reach a resource ceiling, resulting in under-activation relative to young adults. Results from several studies of working memory conform to this pattern (Mattay et al., 2006; Schneider-Garces et al., 2010), including a previously published analysis of a subset of the data described here (Cappell et al., 2010). However, the analyses used by these studies did not permit measurement of the

distinctiveness between neural representations, focusing instead on age differences in overall activation.

How, according to CRUNCH, should neural distinctiveness change with age and task demands? As task demands increase, subjects increasingly rely on specialized neural resources (Jonides et al., 1997; Smith et al., 1996). However, when task demands exceed the capacity of such specialized mechanisms, additional task-general resources may be recruited (Reuter-Lorenz et al., 1999; Rypma et al., 1999). Thus, neural representations of distinct tasks should be highly discriminable when task demands approach the capacity of specialized neural resources: under such conditions, each task should strongly recruit a set of domain-specific mechanisms. In contrast, when task demands are lower than the capacity of such specialized resources, representations of the two tasks should be less discriminable, as neither set of specialized mechanisms is strongly recruited under these conditions. Similarly, task representations should be less distinctive when demands exhaust the capacity of task-specific resources: under such conditions, both tasks should recruit overlapping sets of domain-general neural resources.

Because older adults are thought to reach their resource limits at lower levels of task demand than young adults (Cappell et al., 2010; Schneider-Garces et al., 2010), CRUNCH predicts that the distinctiveness of neural representations should be greater in older adults than young adults when task demands are low. In contrast, when task demands are high, CRUNCH predicts that neural distinctiveness should be higher in young adults than in older adults. While the dedifferentiation hypothesis and CRUNCH predict different patterns of age-related change in neural distinctiveness, the two models are not mutually exclusive. For example, some mental operations (and their neural underpinnings) may be explained best by age-related dedifferentiation; others may follow the pattern predicted by CRUNCH. Indeed, previous research has offered the intriguing possibility that age-related dedifferentiation in sensory cortex degrades inputs

to higher-order processes, leading to compensation in prefrontal and parietal regions (Park and Reuter-Lorenz, 2009).

Although many studies have investigated the effects of aging on neural recruitment, nearly all of these studies relied on univariate measures of brain activation. However, the relationship between such univariate tests and the distinctiveness of neural representations remains unclear. In particular, neural representations of different mental states may be highly distinctive even when these states evoke indistinguishable univariate activation (Dinstein et al., 2008; Peelen et al., 2006). In contrast, recently developed techniques focusing on multi-voxel activation patterns permit more direct investigations of representational distinctiveness (Haynes and Rees, 2006; Norman et al., 2006). Consistent with the dedifferentiation hypothesis, recent studies using this multi-voxel pattern analysis (MVPA) of fMRI data show that neural representations of visual object categories (faces, houses, pseudo-words, and chairs) become less distinctive in old age (Carp et al., 2010b; Park et al., 2010). However, in contrast to the present study, these reports focused on visual perception and provide little insight into age differences in high-level cognition. Further, these studies did not systematically vary levels of task demand, precluding tests of the CRUNCH model.

To compare the predictions of the dedifferentiation hypothesis and CRUNCH, the present study used MVPA to assess the effects of age and task demands on the distinctiveness of the neural representations of verbal and visuospatial working memory. Healthy young and older adults performed verbal and visuospatial working memory tasks in separate scanning runs. Univariate analysis of the verbal working memory data is described in a separate report (Cappell et al., 2010). Here, distinctiveness between the two memory tasks was evaluated separately during memory encoding, maintenance, and retrieval for low, medium, and high memory loads. Following Li and Sikström (2002), we define the neural representation of a mental state as the pattern of activation elicited by that state; neural representations of different states are said to be distinctive to the extent that one can be distinguished from the other.

## *Materials and Methods*

### Participants

Eighteen young adults (mean age 20.9 years, standard deviation 1.63 years, range 18-25, 10 female) and 23 older adults (mean age 68.3 years, standard deviation 6.67, range 61-82, 13 female) participated in the experiment. All participants were right-handed, with normal or corrected-to-normal vision. Participants had no history of head trauma or neurological or psychiatric illness, and a minimum Mini-Mental State Exam (MMSE) score of 25; older adults had a mean MMSE score of 29.2. Informed consent was obtained from all participants; all procedures were approved by the University of Michigan's Institutional Review Board.

### Experimental design

Participants performed delayed verbal and visuospatial item-recognition working memory (WM) tasks in separate runs while fMRI data were acquired. Both tasks were adapted from Reuter-Lorenz and colleagues (2000); the verbal WM task is also described in a previous report on these data (Cappell et al., 2010). Each trial comprised three phases: encoding, maintenance, and retrieval. To minimize colinearity between task phases, durations of the maintenance phase and the inter-trial interval were jittered across trials (Dale, 1999).

During the encoding phase (1.5s), participants were presented with four, five, or seven uppercase letters (verbal task) or the spatial locations of one, two, or three filled circles (visuospatial task). Letters were evenly spaced along an imaginary circle with a radius of 5° centered on the fixation point; spatial locations of the target letters were irrelevant, and there was no requirement for subjects to remember the locations of letters. Circles appeared at randomly chosen positions along imaginary circles with radii of 2.5°, 5°, or 7.5°. The maintenance phase was an unfilled delay with a variable duration of 4 s

(25%), 6 s (25%), 8 s (25%), or 10 s (25%). Finally, during the probe phase (1.5s), a single lowercase letter (verbal task) or circle (visuospatial task) was presented, and participants indicated whether the probe stimulus belonged to the current memory set (match trials; 50%) or did not (non-match trials; 50%). In the verbal task, probe letters always appeared at fixation. Each trial was followed by a variable fixation interval of 1.5 s (50%), 3 s (25%), 4.5 s (12.5%), or 6 s (12.5%). Participants were instructed to respond as accurately as possible and to fixate a centrally presented red dot throughout each run.

Participants completed four runs of the verbal task and four runs of the visuospatial task. Runs were presented in ABBABAAB order; the tasks designated by A and B were counterbalanced across subjects. Each run comprised 24 trials presented in random order; thus, each participant completed 96 trials for each of the two tasks. Fixation intervals of 20 s duration were presented at the beginning of each run, and after the $8^{th}$ and $16^{th}$ trials. All experimental stimuli were presented using EPrime software (Psychology Software Inc., Pittsburgh, PA, USA).

### FMRI data acquisition

Images were acquired using a 3T whole-body MRI scanner (General Electric). Blood oxygenation level dependent (BOLD) images were acquired using a spiral sequence in 43 contiguous axial 3-mm slices, with an in-plane resolution of 3.44 by 3.44 mm (TR=2 sec, TE=30 ms, flip angle=90°, FOV=22 cm, in-plane matrix=64x64 voxels). High-resolution T1-weighted images with the same orientation as the functional scans were collected at the end of the session (TR=10 ms, TE=3.4 ms, flip angle=23°, FOV=24 cm, matrix=256x256 voxels).

### Data analysis

Preprocessing and model estimation were conducted using SPM5 software (Wellcome Department of Cognitive Neurology, London, UK, www.fil.ion.ucl.ac.uk). Subsequent

analysis was performed using custom routines implemented in MATLAB (MathWorks, Inc., Natick, MA, USA) and the R statistical computing language (R Foundation for Statistical Computing, Vienna, Austria).

## FMRI preprocessing

Functional data were corrected for differences in slice time acquisition and realigned to the first volume using standard functions in SPM5. No spatial normalization or smoothing was applied prior to multivariate analysis (Haxby et al., 2001).

## Multi-voxel pattern analysis

We used multi-voxel pattern analysis (MVPA) to measure age differences in the distinctiveness of neural representations of verbal and visuospatial working memory. Neural distinctiveness was estimated using a correlation distance metric (Carp et al., 2010b; Haushofer et al., 2008; Haxby et al., 2001). We selected this metric over alternative multivariate techniques (e.g., support vector machines, neural network classifiers) because its logic and implementation are relatively simple and because it does not require the optimization of as many free parameters. We also note that previous research has documented similar effects using different multivariate analyses. For example, Park and colleagues (2010) showed that correlations between neural distinctiveness and behavioral performance were highly similar whether distinctiveness was measured using correlation distance (as in the present study) or using support vector machines.

We first estimated the neural response for each working memory condition (verbal and visuospatial), task phase (encoding, maintenance, and retrieval), and memory load (low, medium, and high). Activation for even- and odd-numbered runs was estimated using separate regressors (Haxby et al., 2001). Neural responses related to encoding, maintenance, and retrieval were modeled using separate event-related regressors (Postle et al., 2000); this analysis was carried out using the General Linear Model

(Friston et al., 1995) as implemented in SPM5. Only correct trials were included in the analysis; incorrect trials were modeled separately as a nuisance covariate.

Next, we used the activation estimates derived from the GLM analysis described above to assess the distinctiveness between distributed representations of the verbal and visuospatial working memory tasks. To do so, we compared correlations across voxels within and between the verbal and visuospatial tasks, across even- and odd-numbered runs. The distinctiveness between verbal and visuospatial tasks for any given set of voxels was defined as the difference between the mean Fisher-transformed correlations across those voxels' β-values within and between the two tasks (Haushofer et al., 2008; Haxby et al., 2001):

Within-task correlation = $(\text{corr}(\text{verbal}_{\text{even}}, \text{verbal}_{\text{odd}}) + \text{corr}(\text{spatial}_{\text{even}}, \text{spatial}_{\text{odd}})) / 2$
Between-task correlation = $(\text{corr}(\text{verbal}_{\text{even}}, \text{spatial}_{\text{odd}}) + \text{corr}(\text{spatial}_{\text{even}}, \text{verbal}_{\text{odd}})) / 2$
Distinctiveness = Within-task correlation – Between-task correlation

To minimize the contribution of potential age differences in BOLD variability to our results, we used β-values, which are not scaled by model error, rather than *t*-values, for this analysis (Rypma and D'Esposito, 2000). Positive distinctiveness scores indicate that activation patterns distinguished between memory conditions; distinctiveness scores of zero indicate that activation patterns were uninformative with regard to memory conditions.

To generate whole-brain maps of pattern distinctiveness, we combined the correlation analysis described above with a multivariate searchlight procedure (Kriegeskorte et al., 2006). For each voxel in the brain, we identified all voxels within a 12-mm-radius sphere centered on that voxel. This radius was selected to maximize neural distinctiveness across all conditions and age groups (and, thus, to maximize sensitivity to detect between-condition differences in distinctiveness). Next, we calculated the distinctiveness between verbal and visuospatial memory conditions across this group of

voxels. The resulting neural distinctiveness score was then entered as the value for the center voxel. This procedure was iterated across all voxels in the brain, yielding a whole-brain map of neural distinctiveness between the two memory tasks. The neural distinctiveness value at each voxel reflects the discriminability between tasks for the local pattern of activation centered on that voxel. Separate searchlight maps were estimated for each trial phase and memory load. These maps were subsequently normalized into MNI space and averaged within age groups.

### Random-effects analysis

For each of the three trial phases (encoding, maintenance, and retrieval), voxel-wise neural distinctiveness maps were submitted to a two-way mixed ANOVA including a between-subjects factor of age group (young, old) and a within-subjects factor of memory load (low, medium, and high). Voxel-wise *F*-maps were thresholded at a height threshold of $p < 0.005$ and an extent threshold of 50 contiguous voxels (e.g., Daselaar et al., 2003; Miller et al., 2008; Persson et al., 2007).

## *Results*

### Behavioral data

Participants' reaction time (RT) and accuracy data were analyzed using separate mixed ANOVAs with within-subjects factors of task (verbal, visuospatial) and load (low, medium, and high) and a between-subjects factor of age group (young, old). Incorrect and omitted responses were excluded from the RT analysis. RT and accuracy data are presented in Figures 9 and 10, respectively.

Reaction time data revealed a significant main effect of load: RT increased with increasing memory load ($F(2, 39) = 86.85$, $p < 0.001$). The main effect of age group was also significant: older adults responded more slowly than younger adults ($F(1, 39) =$

22.75, $p < 0.001$). We also observed a significant main effect of memory task, such that responses were slower for the verbal task than for the visuospatial task ($F(1, 39) = 22.21$, $p < 0.001$). Finally, we found a significant interaction between age group and memory load: the effect of age on RT increased with memory load ($F(2, 78) = 5.62$, $p = 0.0052$). No additional RT effects reached significance.

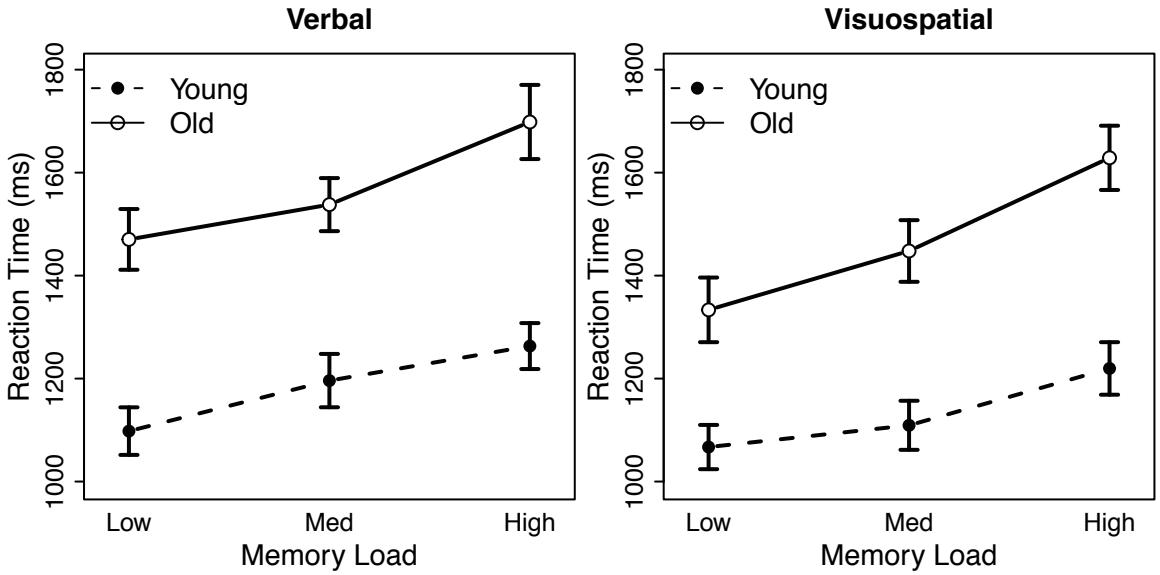



**Figure 9. Effects of age group and memory load on reaction time.**
Left panel: data from the verbal working memory task. Right panel: data from the visuospatial working memory task.

Accuracy data showed a significant main effect of memory load, such that accuracy decreased with increasing load ($F(2, 39) = 67.88$, $p < 0.001$). We also observed a significant interaction between age group and task ($F(2, 39) = 4.34$, $p = 0.016$): older adults showed lower accuracy than young adults for the verbal task ($F(1, 39) = 3.96$, $p = 0.054$), but not for the visuospatial task ($F < 1$, *ns*). No additional accuracy effects were significant.

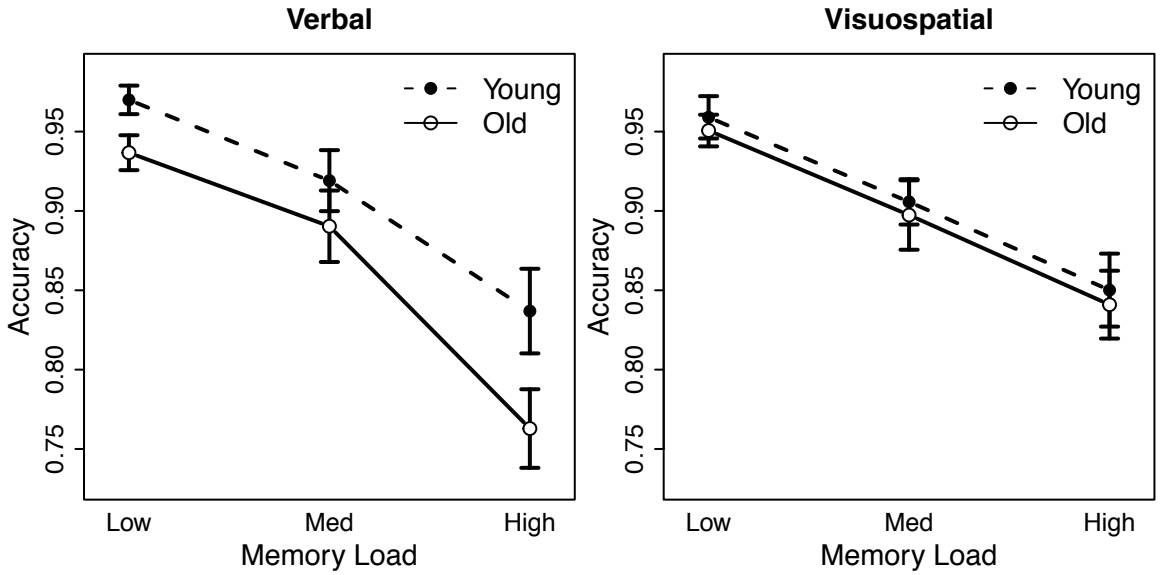



**Figure 10. Effects of age group and memory load on response accuracy.** Left panel: data from the verbal working memory task. Right panel: data from the visuospatial working memory task.

### FMRI data

## Encoding phase

According to the dedifferentiation hypothesis, the distinctiveness of neural representations should be uniformly reduced in old age. To test this view, we measured overall age differences in distinctiveness during memory encoding. Voxel-wise analysis revealed significant main effects of age group in early visual areas, including left striate cortex, right lingual gyrus, and bilateral inferior occipital gyrus (Table 6; Figure 11). We also observed significant effects of age in regions that are thought to play important roles in working memory performance, including left inferior frontal gyrus, right middle frontal gyrus, and left inferior parietal lobule. Inspection of these clusters revealed reduced neural distinctiveness in older adults for each of these clusters (Figure 11). Critically, no regions showed higher neural distinctiveness in older adults than in young adults.

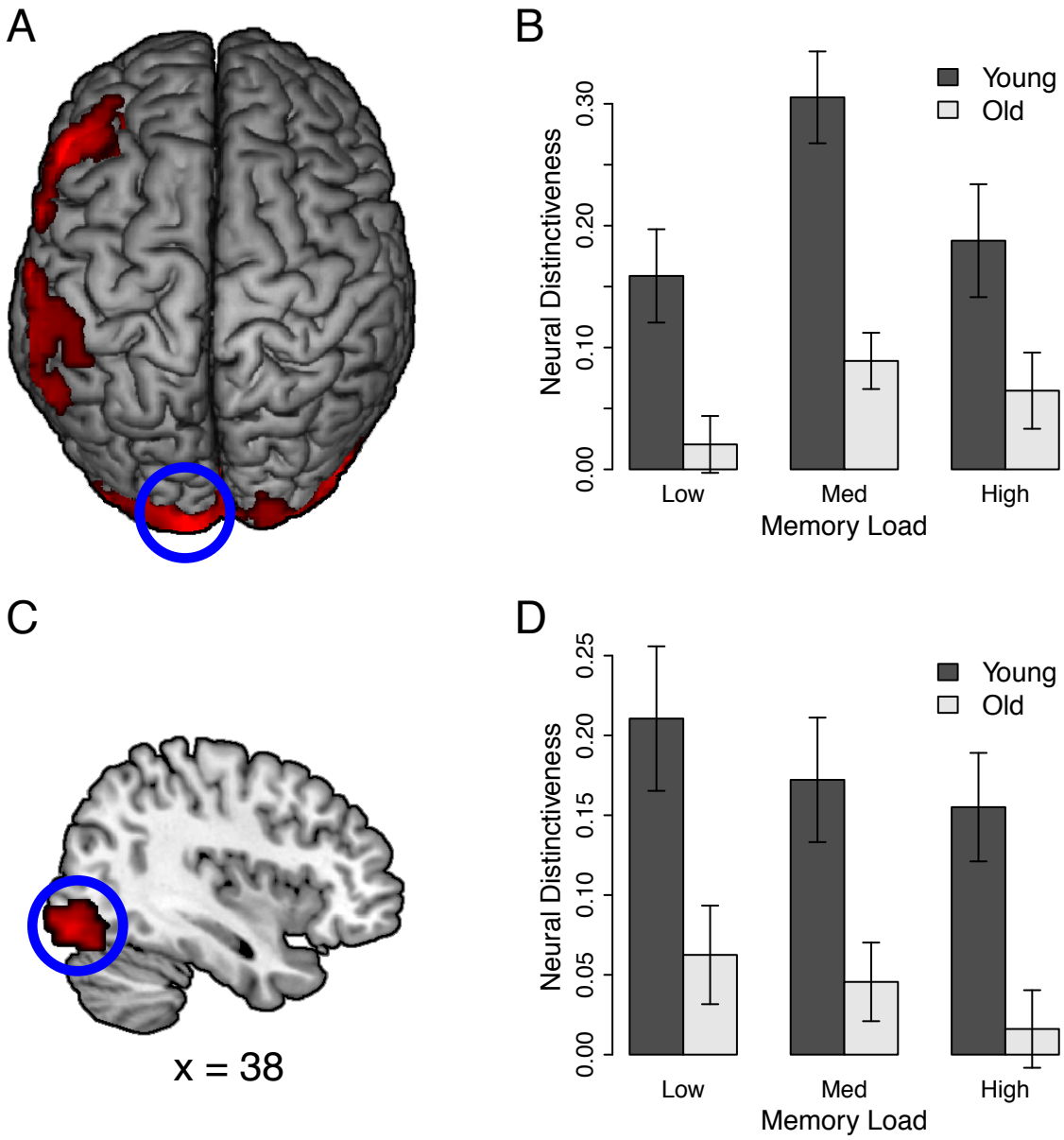



**Figure 11. Main effect of age group during working memory encoding.** See also Table 6, Main Effect of Age. A: Older adults showed decreased distinctiveness between verbal and visuospatial WM tasks in prefrontal, parietal, and sensory cortex. Left striate cortex is highlighted. B: Neural distinctiveness scores from left striate cortex. C: Older adults also showed decreased neural distinctiveness in right inferior occipital gyrus (x = 38). D: Neural distinctiveness scores from right inferior occipital gyrus.

We observed significant interactions between age group and memory load in right middle frontal gyrus, left middle temporal gyrus, and anterior cingulate cortex (Table 6; Figure 12). Inspection of these clusters revealed a consistent pattern, such that neural

distinctiveness increased with memory load in younger adults (all cluster simple effects, *p*s <= 0.07) but decreased with load in older adults (all cluster simple effects, *p*s <= 0.05; Figure 12). Critically, distinctiveness in these regions was equivalent across age groups at low memory load but significantly reduced in older adults at high memory load (all cluster simple effects, *p*s <= 0.05).

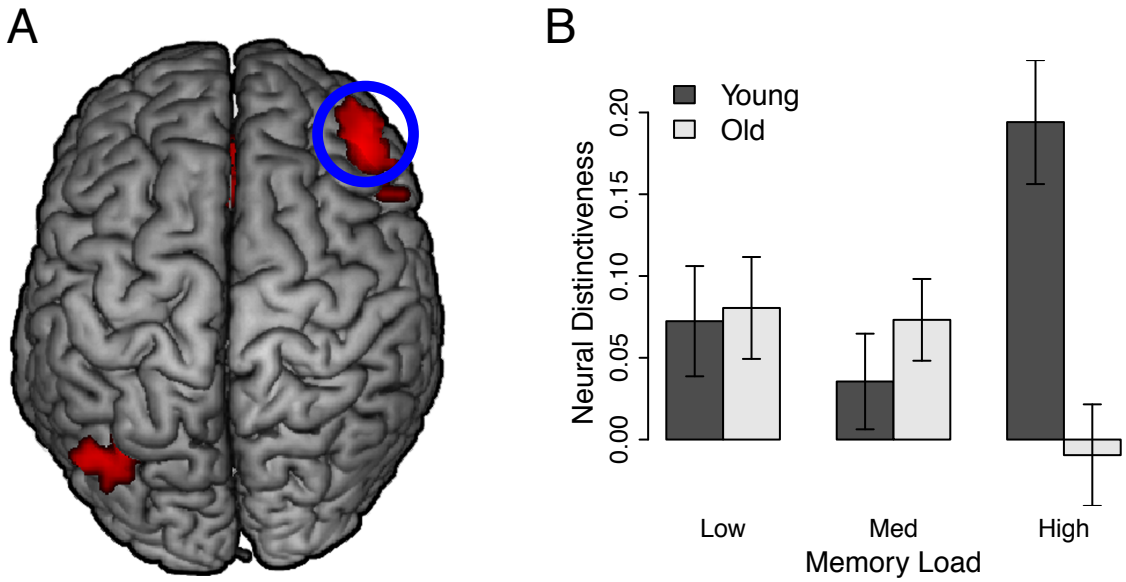



**Figure 12. Age group by load interaction during working memory encoding.** See also Table 6, Age by Load Interaction. A: Neural distinctiveness increased with load in younger adults but decreased with load in older adults in right middle frontal gyrus, anterior cingulate cortex, and left middle temporal gyrus. Middle frontal gyrus is highlighted. B: Neural distinctiveness scores from right middle frontal gyrus.

## Maintenance phase

Next, we measured the effects of age group and memory load on neural distinctiveness during the maintenance phase. In contrast to the encoding phase, overall neural distinctiveness did not vary with age group: no regions showed a significant main effect of age group.

However, we observed age group by memory load interactions across several prefrontal and parietal regions, including orbitofrontal cortex and bilateral superior and inferior

frontal gyrus (Table 7; Figure 13). The left inferior frontal gyrus cluster showed partial overlap with the main effect of age observed during memory encoding (Table 6; Figure 3). Inspection of these results showed a consistent pattern across regions. In each cluster, neural distinctiveness increased with memory load in young adults (all cluster *p*s <= 0.01). In older adults, however, neural distinctiveness tended to decrease with increasing memory load (orbitofrontal cortex, left superior frontal gyrus, left inferior frontal gyrus, right inferior frontal gyrus: *p*s <= 0.05; right superior frontal gyrus, left precuneus: *ns*; Figure 13). Thus, older adults showed greater neural distinctiveness than young adults at low loads (all cluster *p*s <= 0.05) and less distinctiveness than young adults at high loads (all cluster *p*s <= 0.05). These interactions mirror effects observed in the behavioral data: older adults showed the greatest RT impairment at high memory loads.

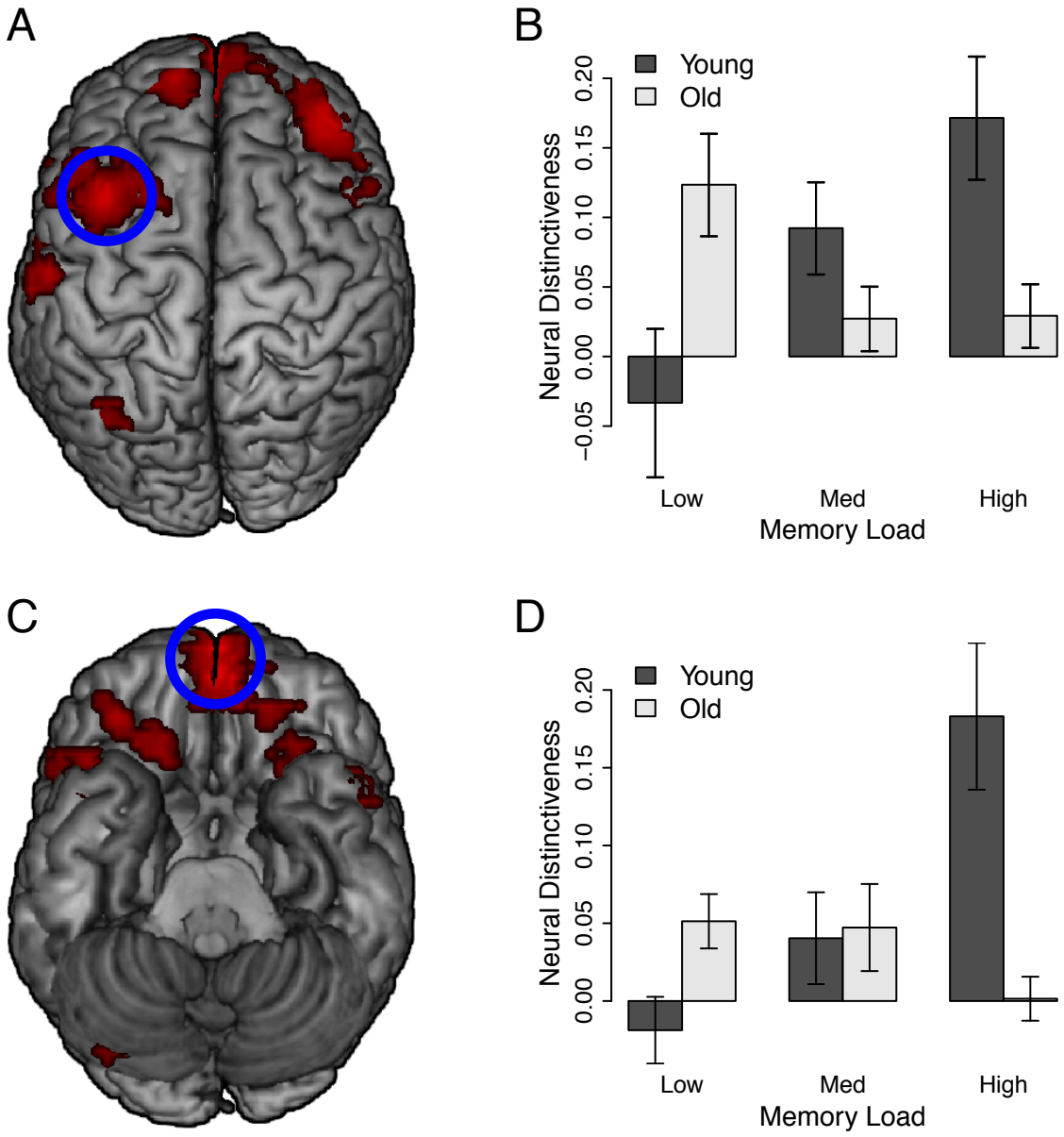



**Figure 13. Age group by load interaction during working memory maintenance.** See also Table 7, Age by Load Interaction. A: Neural distinctiveness increased with load in younger adults but decreased with load in older adults across several prefrontal and parietal clusters. Superior frontal gyrus is highlighted. B: Neural distinctiveness scores from left superior frontal gyrus. Further descriptions of these results are given in Table 7. C: Age by load interactions along the ventral surface of the brain. Orbitofrontal cortex is highlighted. D: Neural distinctiveness scores from orbitofrontal cortex.

## Retrieval phase

Finally, we examined retrieval-phase distinctiveness between verbal and visuospatial conditions as a function of age group and memory load. We observed a significant main effect of age group in left extrastriate cortex, such that neural distinctiveness was reduced in older adults (Table 8). This cluster showed substantial overlap with the main effect of age observed during memory encoding (Table 6; Figure 11). No age by load interactions reached significance in this analysis.

## *Discussion*

The present study measured age differences in the neural representations of memory encoding, maintenance, and retrieval using multi-voxel pattern analysis (MVPA). Results from sensory cortex during memory encoding and retrieval were consistent with age-related neural dedifferentiation: older adults showed reduced distinctiveness between verbal and visuospatial memory conditions, regardless of memory load (Table 6; Figure 11). In contrast, results from memory maintenance were difficult to reconcile with the dedifferentiation hypothesis but consistent with the Compensation-Related Utilization of Neural Circuits Hypothesis (CRUNCH) model (Reuter-Lorenz and Cappell, 2008). During the maintenance phase, neural distinctiveness in prefrontal and parietal regions increased with memory load in young adults. In older adults, this pattern was absent or even reversed. Thus, relative to young adults, older adults showed increased maintenance-related distinctiveness at low memory loads but decreased distinctiveness at high memory loads (Table 7; Figure 13).

Results from visual cortex are broadly consistent with previous research on age-related dedifferentiation. Previous studies have documented age differences in sensory regions during working memory tasks (for reviews, see Park and Reuter-Lorenz, 2009; Reuter-Lorenz and Lustig, 2005). The present results corroborate and extend these reports, suggesting that age differences in sensory activity reflect, at least in part, changes in representational distinctiveness. Our findings dovetail with recent studies showing age-

related declines in the distinctiveness of neural representations of visual objects (Carp et al., 2010b; Park et al., 2010). Our results are also consistent with single-unit recording studies showing inefficient perceptual representations of simple visual stimuli in senescent monkeys (Leventhal et al., 2003; Schmolesky et al., 2000) and cats (Hua et al., 2006). Furthermore, these findings confirm prior research showing that object representations in prefrontal and parietal cortex become less discriminable in old age (Carp et al., 2010), suggesting that age-related dedifferentiation is not restricted to ventral visual cortex. Finally, our results are generally consistent with reports of hemispheric specialization of motor (Hutchinson et al., 2002; Mattay et al., 2002) and auditory (Bellis et al., 2000) representations in old age (although, to our knowledge, no published work has investigated age differences in the distinctiveness of these representations using the multivariate approach described here).

However, results from memory maintenance do not support the view that representational distinctiveness is uniformly reduced in older adults. Indeed, no brain regions exhibited a significant main effect of age group during the maintenance phase. Instead, relative to young adults, older adults showed increased distinctiveness at low memory loads and decreased distinctiveness at high loads (Figure 5). Consistent with this observation, analysis of the reaction time data revealed that older adults were most impaired at high memory loads. These results are consistent with CRUNCH, which posits that older adults must recruit more neural resources than young adults to maintain performance for a given level of task difficulty. Thus, when task demands are low, older adults engage more task-specific resources than young adults. However, older adults are more likely than young adults to reach their resource limitations when task demands are high, leading to increased reliance on auxiliary task-general mechanisms and, in consequence, decreased distinctiveness between task representations. These results show that dedifferentiation is not a general property of the aging brain: depending on the level of task demand, older adults can show higher or lower neural differentiation than young adults.

These results complement and extend previous studies of age by memory load interactions on neural recruitment. For example, studies of working memory using univariate analysis of fMRI (Cappell et al., 2010; Mattay et al., 2006; Schneider-Garces et al., 2010) and EEG (McEvoy et al., 2001) data have documented age-related over-activation at low memory load and under-activation at high memory load. Unlike the present findings, these previous results do not speak to the distinctiveness or fidelity of task representations. Nevertheless, consistent with our results, they show that increases in task demand can have opposing effects on neural recruitment in young and elderly populations.

As reviewed above, previous studies have reported neuroimaging evidence consistent with age-related dedifferentiation (Carp et al., 2010b; Park et al., 2010) and with the CRUNCH model (Cappell et al., 2010; Mattay et al., 2006). However, prior support for the two models has been obtained in different studies, using different subjects and experimental paradigms. Here, in a single experiment, we show that sensory responses during memory encoding and retrieval were consistent with age-related dedifferentiation, whereas prefrontal and parietal responses during memory maintenance supported the CRUNCH model. Thus, we argue that healthy aging has divergent effects on different mental operations that subserve working memory. These results are consistent with a recent review by Rajah and D'Esposito (2005), which showed that different regions of prefrontal cortex undergo different patterns of age-related change. While both dedifferentiation and the CRUNCH model can account for certain aspects of our results, neither theory is sufficient to explain the overall pattern of results.

The present study investigated age differences in the distinctiveness of intra-regional representations, focusing on fine-scale activation patterns in local neighborhoods of voxels. In contrast, previous neuroimaging studies have documented age-related dedifferentiation of inter-regional neural representations, focusing on differences between distant brain regions (for a review, see Reuter-Lorenz and Park, 2010). In

particular, as reviewed by Cabeza's (2002) hemispheric asymmetry reduction in older adults (HAROLD) model, many studies have reported that tasks that evoke lateralized activation in young adults tend to evoke bilateral activation in older adults. The age-related reductions in neural distinctiveness that we observed during memory encoding and retrieval accord with the HAROLD model: both show that the neural substrates of different cognitive states become more similar in old age. However, the present results may not reflect the same phenomenon documented by HAROLD: age-related dedifferentiation of intra- and inter-regional activation patterns may or may not stem from a common mechanism.

In contrast to prior reports, the present study focuses on age differences in neural representation, rather than differences in overall activation. The interpretation of age differences in activation has proven contentious: age-related over-activation in frontal and parietal cortex has been hypothesized to reflect both compensation and impairment (Reuter-Lorenz and Lustig, 2005). In contrast, MVPA measures the information present in patterns of neural activation (Haxby et al., 2001; Haynes and Rees, 2006; Norman et al., 2006), simplifying the interpretation of age differences. If neural distinctiveness is reduced in older adults, we can conclude that activation patterns in these subjects convey less information than those in young adults; if older adults show increased distinctiveness, we can conclude that their activation patterns are more informative than those of young adults. Thus, the use of MVPA in this study helps to mitigate the interpretive ambiguities associated with the analysis of age differences in average BOLD response. Nevertheless, MVPA has its limitations: while this method can reveal whether neural activation patterns are discriminable, it does not explain the way these activations differ, or the computational mechanisms underlying the observed results.

While our analysis focused on the effects of task demand in the context of working memory, our results may generalize to other processes as well. For example, increasing demand on task-switching or interference resolution mechanisms may also lead to

decreased neural distinctiveness in older adults. Future studies should examine these issues to determine the generality of our results.

In summary, the present study charts the effects of healthy aging on neural representations of working memory. Our results provide partial support for both age-related dedifferentiation and the CRUNCH model. Critically, though, neither model can explain the full range of effects present in the data. We suggest that hybrid models, incorporating aspects of both dedifferentiation and compensation, will be necessary to account for the complex pattern of neuro-cognitive change associated with healthy aging.

## Tables.

### Table 6. Encoding-related neural distinctiveness.

| Region | Number of voxels | MNI coordinates | | | Neural distinctiveness | | | | Statistics |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Age group | Memory load | | | |
| | | *X* | *Y* | *Z* | | Low | Med | High | |
| *Main Effect of Age* | | | | | | | | | |
| L. inferior frontal gyrus | 431 | -47 | 28 | 15 | Young | .16 | .19 | .28 | $F(1, 117) = 23.46$, $p < .001$ |
| | | | | | Old | .04 | .05 | .03 | |
| R. middle frontal gyrus | 56 | 24 | 48 | 12 | Young | .07 | .11 | .11 | $F(1, 117) = 13.75$, $p < .001$ |
| | | | | | Old | .02 | .01 | -.05 | |
| L. inferior parietal lobule | 204 | -55 | -31 | 39 | Young | .07 | .13 | .14 | $F(1, 117) = 10.78$, $p < .001$ |
| | | | | | Old | .03 | .01 | -.01 | |
| L. striate cortex | 1144 | -7 | -100 | -3 | Young | .16 | .31 | .19 | $F(1, 117) = 25.65$, $p < .001$ |
| | | | | | Old | .02 | .09 | .06 | |
| L. inferior occipital gyrus | 1144 | -31 | -89 | -18 | Young | .13 | .20 | .16 | $F(1, 117) = 18.36$, $p < .001$ |
| | | | | | Old | .04 | .05 | .05 | |
| R. lingual gyrus | 1144 | 17 | -86 | -12 | Young | .25 | .21 | .27 | $F(1, 117) = 18.98$, $p < .001$ |
| | | | | | Old | .13 | .09 | .08 | |
| R. inferior occipital gyrus | 1144 | 38 | -86 | -15 | Young | .19 | .16 | .15 | $F(1, 117) = 19.94$, $p < .001$ |
| | | | | | Old | .07 | .04 | .00 | |
| *Age by Load Interaction* | | | | | | | | | |
| R. middle frontal gyrus | 267 | 41 | 34 | 18 | Young | .07 | .04 | .19 | $F(2, 117) = 10.52$, $p < .001$ |
| | | | | | Old | .08 | .07 | -.01 | |
| L. middle temporal gyrus | 103 | -41 | -65 | 30 | Young | .04 | .20 | .20 | $F(2, 117) = 9.11$, $p < .001$ |
| | | | | | Old | .10 | .05 | .01 | |
| Anterior cingulate cortex | 66 | 10 | 31 | 27 | Young | .06 | .01 | .18 | $F(2, 117) = 7.17$, $p < .001$ |
| | | | | | Old | .03 | .08 | .01 | |

**Table 7. Maintenance-related neural distinctiveness.**

| Region | Number of voxels | MNI coordinates | | | Neural distinctiveness | | | | Statistics |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Age group | Memory load | | | |
| | | *X* | *Y* | *Z* | | Low | Med | High | |
| *Main Effect of Age* | | | | | | | | | |
| No significant clusters | | | | | | | | | |
| *Age by Load Interaction* | | | | | | | | | |
| Orbitofrontal cortex | 523 | 0 | 55 | -15 | Young | -.02 | .04 | .18 | $F(2, 117) = 13.48$, $p < .001$ |
| | | | | | Old | .05 | .05 | .00 | |
| L. superior frontal gyrus | 171 | -38 | 17 | 54 | Young | -.03 | .09 | .17 | $F(2, 117) = 11.72$, $p < .001$ |
| | | | | | Old | .12 | .03 | .03 | |
| L. inferior frontal gyrus | 323 | -47 | 10 | 21 | Young | -.02 | .07 | .11 | $F(2, 117) = 9.48$, $p < .001$ |
| | | | | | Old | .09 | .03 | .03 | |
| L. inferior frontal gyrus | 161 | -24 | 31 | -3 | Young | -.02 | .14 | .21 | $F(2, 117) = 7.87$, $p < .001$ |
| | | | | | Old | .13 | .06 | .07 | |
| R. superior frontal gyrus | 429 | 41 | 38 | 33 | Young | .05 | .06 | .21 | $F(2, 117) = 10.24$, $p < .001$ |
| | | | | | Old | .13 | .11 | .09 | |
| R. inferior frontal gyrus | 429 | 38 | 24 | 12 | Young | -.06 | .03 | .14 | $F(2, 117) = 15.46$, $p < .001$ |
| | | | | | Old | .09 | .00 | .01 | |
| L. precuneus | 85 | -17 | -58 | 33 | Young | -.02 | .07 | .16 | $F(2, 117) = 8.45$, $p < .001$ |
| | | | | | Old | .08 | .06 | .05 | |

**Table 8. Retrieval-related neural distinctiveness.**

| Region | Number of voxels | MNI coordinates | | | Neural distinctiveness | | | | Statistics |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Age group | Memory load | | | |
| | | *X* | *Y* | *Z* | | Low | Med | High | |
| *Main Effect of Age* | | | | | | | | | |
| L. extrastriate cortex | 192 | -21 | -103 | 9 | Young | .22 | .22 | .20 | $F(1, 117) = 22.09$, $p < .001$ |
| | | | | | Old | .09 | .05 | .08 | |
| *Age by Load Interaction* | | | | | | | | | |
| No significant clusters | | | | | | | | | |

# Chapter 5: Discussion

Computational models of cognitive aging have argued that age differences in the distinctiveness of neural representations play a critical role in age differences in cognitive performance (Li et al., 2000; Li et al., 2001). In particular, Li and colleagues have argued that a range of cognitive impairments associated with aging stem from changes in dopaminergic function resulting in decreased signal-to-noise ratio (SNR) and decreased distinctiveness of neural representations. Li and others have cited studies of ability dedifferentiation as support for this theory. Specifically, a range of studies have claimed that cross-subject correlations in performance across tasks increase across the adult lifespan; proponents of the dedifferentiation hypothesis argue that these changes in the structure of cognitive ability reflect age-related decreases in representational fidelity. However, as described in Chapter 1, these effects have proven inconsistent, with many published studies showing null and even reversed effects. And while recent neuroimaging studies have investigated age differences in neural distinctiveness, these studies have focused on high-level visual perception, and have used analytic strategies that do not capture the full range of information encoded in distributed patterns of neural activation. Thus, the present studies were undertaken to test the dedifferentiation hypothesis using more direct and more accurate measures of representational fidelity.

The present studies also compared the dedifferentiation hypothesis with alternative accounts of cognitive aging. In particular, while some theories of aging attribute differences in neural activation to age-related impairments, others propose that some of these changes reflect compensation for other impairments. In other words, competing theories disagree about which age-associated changes are the underlying causes of cognitive decline and which are the consequences. These issues have proven to be contentious, with divergent results across studies. For example, while Cabeza and

colleagues (2002) have argued that increased bilateral activation in old age is associated with improved performance and thus reflects compensation for impairment, Duverne et al. (2009) reported that such bilateral activation is associated with poorer performance and reflects impaired prefrontal function. Previous studies of impairment and compensation in old age have generally focused on measures of average regional activation; the present studies sought a novel perspective on this debate by focusing on measures of information (i.e., the degree to which multi-voxel activation patterns discriminated among task conditions) rather than average activation.

This report presents three studies of age differences in the fidelity of neural representations. Study 1 demonstrated that neural representations of high-level visual categories (i.e., faces and houses) are less distinctive in older adults, relative to young adults. Specifically, classification of stimulus category by brain activation was less accurate among older adults, both using data from ventral visual cortex and across a network of brain regions sensitive to object category. Results were consistent with the dedifferentiation hypothesis. Multi-voxel activation patterns in the ventral visual cortex and throughout a network of brain regions sensitive to visual object categories were less informative about task conditions in older adults than in young adults. Furthermore, inconsistent with compensation-based accounts of cognitive aging, no brain regions were more sensitive to object category in older adults relative to young adults, and the spatial distribution of object representations across the brain was similar in young and older adults. Study 2 took an analogous approach to investigating age differences in the motor system. Results indicated age-related declines in the fidelity of motor representations: multi-voxel activation patterns evoked by right- and left-hand movement were less distinctive in older adults than in young adults throughout the motor system. No regions showed greater distinctiveness in older adults than in young adults, also consistent with the dedifferentiation hypothesis but inconsistent with compensation accounts. Finally, Study 3 investigated age differences in neural representations of visual and spatial working memory. Results from memory encoding and retrieval were largely consistent with Studies 1 and 2, revealing lower-fidelity task

representations in older adults in sensory and frontal regions. In contrast, results from memory maintenance showed interactions between age group and task demands, such that representational specificity increased with task demands in young adults but decreased with task demands in older adults.

Overall, results from sensory and motor tasks were consistent with the dedifferentiation hypothesis of cognitive aging: multi-voxel activation patterns of visual stimuli and motor actions were less distinctive in older adults than in young adults. These results are challenging to explain in terms of compensation. Compensation accounts would predict that older adults should make up for reduced representational fidelity in impaired regions through increased representational fidelity elsewhere--for example, by engaging more bilateral (Cabeza, 2002) or more anterior regions (Davis et al., 2008). And older adults with especially poor representational distinctiveness in sensory areas should show particularly high distinctiveness in frontal regions. However, these predictions were not supported in Studies 1 or 2: both studies showed uniformly reduced distinctiveness of visual and motor representations in old age.

In contrast, results from working memory maintenance in Study 3 were challenging to explain in terms of the dedifferentiation hypothesis but more consistent with compensation-based accounts. The dedifferentiation hypothesis predicts reduced representational fidelity in old age and does not make specific predictions about different tasks or varying levels of difficulty. However, while results from working memory maintenance revealed reduced distinctiveness in older adults under high task load, older adults actually showed greater distinctiveness than young adults under low load conditions. This pattern of results is consistent with the view, advanced by the CRUNCH model, that older adults recruit domain-general resources under high task demands to compensate for underlying impairments. Specifically, as task difficulty increases, older adults are increasingly forced to rely on the same domain-general resources for both verbal and spatial working memory. As the neural representations of the two task domains converge under high load, the distinctiveness of the multi-voxel

activation patterns evoked by the two tasks shrinks. This pattern of results is consistent with previous neuroimaging studies showing analogous age-by-load interactions (although these studies focused on average activation, not representational distinctiveness). In particular, several studies using fMRI (Cappell et al., 2010; Mattay et al., 2006) and EEG (McEvoy et al., 2001) have documented positive associations between load and prefrontal activation in young adults but negative associations between load and activation in older adults.

In sum, the present studies provide novel support for the dedifferentiation hypothesis of cognitive aging, using relatively direct measures of representational fidelity to achieve a reliability that has so far eluded more distant behavioral assays. These results also argue against age-related compensation in sensory and motor regions. However, the present results also constrain the reach of the dedifferentiation hypothesis to simple sensory and motor tasks. In particular, the results of Study 3 are challenging to reconcile with age-related dedifferentiation and are more in line with compensation-based models. Thus, the present results suggest that new theories incorporating aspects of both dedifferentiation and compensation will be needed to achieve a more complete understanding of the aging brain.

### *Relationship with other forms of dedifferentiation*

Although the present studies were inspired by the behavioral literature on ability dedifferentiation, the relationship between the behavioral measures used in that literature and the physiological measures used here remains unclear. The conceptual link between behavioral and neural dedifferentiation is somewhat tenuous. Studies of behavioral dedifferentiation focus on diverse batteries of cognitive tests and examine correlations in performance across subjects. In contrast, studies of neural dedifferentiation, including the studies reported here, focus on a single task and analyze task-evoked neural activity within subjects, rather than between subjects. In addition,

studies of behavioral and neural dedifferentiation use different sampling methods. Behavioral studies tend to use large, representative samples, with a mixture of cross-sectional and longitudinal designs. In contrast, neuroimaging studies on this topic tend to use much smaller samples, and to use cross-sectional designs.

Further, as reviewed above, evidence on behavioral age-related dedifferentiation is mixed, with many studies showing similar correlational structures of abilities across the lifespan. In contrast, all three studies presented here are consistent with age-related declines in neural specificity, and independent research groups have published conceptual replications (Payer et al., 2006; Voss et al., 2008) of this basic finding. So perhaps behavioral dedifferentiation is a spurious finding--a chance false positive or an artifact of flawed sampling or analytic procedures--while neural dedifferentiation is a bona fide phenomenon. This would be ironic, since studies of the latter phenomenon were inspired by studies of the former.

Overall, the conceptual and methodological differences between studies of behavioral and neural dedifferentiation suggest that the two sets of (putative) effects may reflect different underlying phenomena. Future studies should investigate this issue by measuring both effects in the same sample.

It is also tempting to draw analogies between the phenomena documented here and other age differences in neural activity. For example, Garrett and colleagues (2010) have reported that variability in task-orthogonal brain activation is a powerful predictor of age--in fact, a stronger predictor than mean activation. Further, Garrett et al. (2013) have demonstrated that neural variability was less variable across different levels of task demand in older adults than in young adults. These authors have linked their findings both to ability dedifferentiation (i.e., age-related increases in correlations across tasks) and to the age differences in neural decoding reported here. This work raises the fascinating possibility that age differences in neural decoding of sensorimotor and cognitive states, and task-related modulation of signal variability all reflect a single

phenomenon. However, much as discussed above, these phenomena have been documented in separate studies using different samples, task protocols, and analysis procedures.

Similarly, as reviewed above, previous studies have argued that aging is associated with reduced lateralization of brain activation. For example, Reuter-Lorenz and colleagues (Reuter-Lorenz et al., 2000) showed that verbal and spatial working memory tasks evoke left- and right-lateralized prefrontal activation, respectively, in young adults, but evoke bilateral activation in older adults. Similarly, Cabeza and colleagues (Cabeza et al., 2002) reported left-lateralized activation during a verbal working memory task in young adults but bilateral activation in older adults. As with Garrett's findings of age differences in neural signal variability (Garrett et al., 2010, 2013), these results invite comparison with the present findings: perhaps both reflect a shared cause. Again, however, these phenomena have been assessed using very different analytic procedures. Studies of age differences in lateralization focus on interactions between age, hemisphere, and task on average regional activation. In contrast, studies of age differences in neural decoding performance (including the present studies) examine multi-voxel activation patterns within much smaller regions; for example, searchlight analyses in the present studies used radii of 10 to 12 mm. And again, these phenomena have been only been investigated so far in separate samples.

In sum, a number of potentially distinct phenomena have been associated with the blanket term of age-related dedifferentiation, but none have been investigated within the same study. While an integrated account of many or all of these phenomena holds great appeal, the current literature does not support such an account. Additional research will be required to determine the shared or separate origins of these effects.

### *Limitations and future directions*

The present studies set out to test the dedifferentiation hypothesis of cognitive aging; results from sensory and motor tasks were largely consistent with this account. Nevertheless, it is important to point out the limitations of these results, and the directions future studies should take to increase confidence in the conclusions.

All three studies relied on relatively small samples of unusual participants. Meta-analytic research shows that most studies in the social science literature in general, and in the neuroimaging literature in particular, are underpowered (Yarkoni, 2009); underpowered studies are known to increase rates of false positive and inflated effects (Ioannidis, 2005, 2008). The fact that the three studies in this report came to similar conclusions on this point argues that the effects documented here are genuine. Likewise, complementary evidence from independent labs (Payer et al., 2006; Voss et al., 2008) enhances the visibility of the present findings. However, combining several small studies is no substitute for conducting a properly powered experiment; publication bias may mask null results, leading to an artificial consensus in the published literature (Ioannidis, 2005).

The present studies were also conducted using both unusual young adults and unusual older adults (Henrich et al., 2010). Young adult participants were students at selective universities with high median family incomes. Likewise, older adults were drawn from university towns, meaning that retired professors and doctors were likely over-represented. Finally, these studies used cross-sectional designs, meaning that observed effects may be confounded with cohort differences. It remains an open question how the present results would generalize to representative samples of young and older adults or to a longitudinal design. Interestingly, Nyberg and colleagues (2010) have reported qualitatively different results with regard to age differences in neural activation for cross-sectional versus longitudinal designs, suggesting that longitudinal designs may be needed to achieve accurate results.

The present studies also focused on a small set of cognitive tasks and analytic strategies, further limiting the generality of the conclusions. We found that aging was associated with decreased specificity of neural representations of high-level visual categories (i.e., faces and houses). But it remains unclear whether the present conclusions apply to different domains of visual perception, such as spatial frequency, line orientation, and visual motion. Similarly, the present results do not speak to age differences in neural representations of hearing, touch, or taste. While behavioral studies suggest age differences in perception for these domains, additional research using brain imaging methods will be required to establish the generality of the findings presented here. The present studies also focused on pattern classification of fMRI data as the key measure of neural specificity. Again, the generality of these results across alternative imaging modalities (EEG, TMS, etc.) and analysis methods (sensory adaptation, partial least squares, etc.) remains uncertain. Extending the present results across methods would also increase confidents that these results are not specific to artifacts of hemodynamic imaging. For example, age-related changes in vascular function may alter BOLD responses independent of true neural activity (D'Esposito et al., 1999), and age differences in the shape and variability of the hemodynamic response may artificially inflate (or default) age differences in neural specificity (Aizenstein et al., 2004; Buckner et al., 2000).

To address these limitations, future studies should repeat the experiments reported here (1) using well-powered designs, (2) representative samples, (3) longitudinal designs, and (4) a diverse range of data collection and analysis protocols. Some studies have already began to pursue these directions; Goh and colleagues have found results comparable to Study 1 using fMRI adaptation (Goh et al., 2010), and Burianová et al. (2013) have done the same using partial least square analysis. However, much work remains to be done on this front to confirm the generality of these findings.

## *Ongoing research*

In combinations with the results reported by Park and colleagues (2004), the present studies suggest that dedifferentiation of perceptual and cognitive representations are a core feature of the aging brain. However, these results are agnostic with regard to the mechanisms that give rise to age-related dedifferentiation. A series of studies by Leventhal and colleagues suggests that age differences in the production of the inhibitory neurotransmitter GABA play an important--and perhaps causal--role in age-related declines in representational fidelity. Using single-neuron recording techniques in non-human animals, these investigators reported age differences in the encoding of visual information that parallel reports of age-related dedifferentiation in humans. Specifically, Schmolesky and colleagues (2000) found that single-neuron tuning curves for the orientation and movement direction of drifting grating stimuli were substantially less selective in aging macaques than in young adult macaques. This research group has reported analogous results in cats (Hua et al., 2006) and rats (Wang et al., 2006). Hypothesizing that age differences in single-neuron tuning curves were linked with selective losses of GABA-producing neurons, Leventhal and colleagues (2003) measured single-cell selectivity profiles before and after the application of GABA or a GABA agonist directly to the visual cortex. These investigators showed that selectivity for visual orientation and movement direction in elderly macaques was nearly stored to levels seen in young adults following the application of GABA. Providing further support for the role of GABA in maintaining visual representations, they also showed that the application of a GABA antagonist to the visual cortex of young adult macaques strongly suppressed visual selectivity.

Recent studies suggest that similar mechanisms may be at work in aging humans. For example, Betts and colleagues (2005) used visual psychophysical testing to demonstrate that center-surround inhibition is reduced in old age. Because center-surround inhibition is thought to rely on GABA signaling, these investigators speculated that age differences in the neural representation of visual information may stem from

losses of GABA-producing neurons. These investigators (Betts et al., 2009) and others (Karas and McKendrick, 2011) have replicated these behavioral effects. Nevertheless, because none of these studies directly assessed GABA signaling in the brain, their results do not definitively establish a link between GABA and age-related visual impairment. Neuroimaging (Grachev and Apkarian, 2001; Sanacora et al., 2004) and post-mortem (Pinto et al., 2010) research on humans also suggests that GABA function declines across the adult lifespan. However, these studies did not measure perceptual or cognitive performance. Finally, recent studies have linked individual differences in GABA to differences in visual (Edden et al., 2009) and motor (Boy et al., 2010) performance, but only in samples of healthy young adults. Altogether, while previous studies have linked aging with reductions in GABA and individual differences in GABA with cognitive performance, no studies appear to have directly investigated the role of GABA in age-related cognitive impairment.

Thus, continuing research in the lab will directly test the view that age differences in the fidelity of visual representations are linked to age differences in GABA signaling. Specifically, this study will assess the relationship between individual differences in GABA availability and a battery of visual psychophysical tasks. Psychophysical testing will focus on perceptual abilities that have previously been shown to decline with age, including face perception and memory (Bowles et al., 2009; Germine et al., 2011), the detection and discrimination of moving stimuli (Bennett et al., 2007; Billino et al., 2008), and the detection of visual contours (Del Viva and Agostini, 2007; Roudaia et al., 2008). This research will also include a range of standard neuropsychiatric tests of fluid and crystallized intelligence. I predict that individual differences in GABA will partly or fully explain differences in visual perception between young and older adults. I further hypothesize that individual differences in GABA among older adults will significantly predict individual differences in performance. In other words, I predict that controlling for individual differences in GABA will reduce both group and individual differences in performance.

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