FUNCTIONAL CONNECTIVITY AND DEDIFFERENTIATION OF FUNCTION IN OLDER ADULTS DURING CATEGORY MEMBER GENERATION

By

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To my family for their love and support

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Abstract of Thesis Presented to the Graduate School
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Older adults demonstrate a dedifferentiation of function whereby their cognitive abilities become more strongly related over time. Since the time of Spearman this phenomenon has been shown with large samples and multivariate analyses. However, it is not clear what causes this phenomenon at the neural level. Functional neuroimaging has shown that older adults show greater activity and in more areas than young adults during the same cognitive task (termed the HAROLD phenomenon). However, this change in activity does not mean a dedifferentiation of *function* per se. The present investigation is a secondary analysis of a project designed to study the HAROLD phenomenon (Hemispheric Asymmetry Reduction in OLD adults) during category member generation. Here, we used functional connectivity (FC) to measure the level of synchrony and coherence between active regions to investigate whether and how HAROLD occurrences reflect of dedifferentiation of function.

Twenty-two young (16-35 years old), eleven young-old (65-68), and eleven old-old (69-84) adults completed a block fMRI paradigm silently generating category exemplars (17 seconds/category; 16 categories). FMRI data were analyzed using AFNI.

Results show that young-old adults demonstrate HAROLD-consistent activation during the task but that active regions are not strongly related functionally. Old-old adults, on the other

hand, demonstrated widespread functional connections among (almost) all active regions. This suggests that in late life, HAROLD-typical activation is accompanied by functional dedifferentiation but that this stage is preceded by a stage where HAROLD activation occurs in the absence of functional integration of the active areas. We discuss these findings with three possible explanations. One describes the findings in the context of the brain recruiting more neural resources to account for age-related declines. The second possibility discusses the findings as a result of age-specific loss of dopamine receptors. The third possibility discusses the findings as the inability of the thalamus to selectively activate cortical networks needed for the task.

CHAPTER 1
INTRODUCTION

The idea that we can think of human cognition as both one core construct as well as many distinct aptitudes comes from Spearman (Spearman, 1904) who proposed a general factor of intelligence, g, as the degree of positive manifold (i.e. patterns of positive correlations) between tests of different cognitive abilities (S. C Li & Lindenberger, 1999) and posited that the factor structure of cognitive abilities varies with age and ability level (Spearman, 1927). Since the time of Spearman it has been shown that abilities do indeed differentiate (i.e. become less related) in adolescence (Garrett, 1946) and then dedifferentiate in old age (Balinksy, 1941). Dedifferentiation remains one of the most studied and most disputed phenomena in the field of cognitive aging.

There are two main approaches to studying dedifferentiation. The first, termed the "macroapproach" (T. A. Salthouse, 2000), uses large samples, multivariate designs, and correlational analyses to investigate patterns of relationships among variables. These methods have supported dedifferentiation by showing (a) age-related increases in the correlations between levels of performance on cognitive abilities (P. B. Baltes & Lindenberger, 1997; de Frias, 2007; Ghisletta & Lindenberger, 2003; Hayslip & Sterns, 1979), (b) age-related increases in correlations among cognitive changes, (c) higher interindividual variability in change in the older age groups (de Frias, 2007), and a weaker factor structure among measures (P. B. Baltes, Cornelius, S.W., Spiro, A., Nesselroade, J.R., Willis, S.L., 1980). However, other studies have failed to show these patterns (Anstey et al., 2003; Sims, 2008; Tucker-Drob & Salthouse, 2008; Zelinski & Lewis, 2003). Possible explanations for the inconsistencies in the literature include differences in (a) sample age ranges, (b) the cognitive measures included in the analyses, and (c) the types of statistical corrections used (T. A. C. Salthouse, F.I.M., 2000; Sims, 2008). While

macroapproaches have the advantage of greater statistical power and multivariate techniques, they are less able to identify specific mechanisms and processes and require greater inference in order to be translated into applications for neuropsychology and cognitive neuroscience. “Microapproaches”, on the other hand, tend to focus on the age-related effects on a few, more focused variables and use smaller, more extreme groups (e.g. young and old) and are better able to support specific mechanisms. This method has been less utilized in the study of dedifferentiation and was the approach taken by the present investigation.

The general interpretation of dedifferentiation in old age is that the increase in correlations between abilities reflects declines in basic cognitive structures (Zelinski & Lewis, 2003), a pattern that is likely to emerge if the efficiency of an underlying structure or process is low (Deary, 1996; T. A. Salthouse, 2000). Though the exact nature of this factor or process is not known, several theories have been offered. Salthouse and colleagues (Salthouse et al., 1996) proposed that age-related declines are due to a general slowing of processing speed, perhaps as a result of slower speeds of action potentials along single or multiple pathways, faulty neurotransmitters, or reduced synchronization of activation patterns. Li’s neurocomputation model (S. C. Li et al., 2006; S. C Li & Lindenberger, 1999; S. C. Li et al., 2001) proposed that deficient neuromodulation of catecholamines (dopamine, epinephrine, norepinephrine), known to confine neural activity (Oades, 1985; Sawaguchi & Goldman-Rakic, 1991), causes undifferentiated cortical representations and causes an increase in random variability.

These potential mediating factors have been explored independently of the dedifferentiation phenomenon and have only been inferred to be mediating variables. In fact, there is a noticeable lack of “micro” studies that investigate dedifferentiation mechanisms, probably because dedifferentiation is traditionally conceptualized as a multivariate phenomenon

and difficult to conceptualize by studying a small number of cognitive variables. However, one possibility is that dedifferentiation is related to a decrease in functional specialization in old age and that a given brain region might be able to contribute to several different cognitive processes or the same cognitive process could be controlled by multiple neuroanatomical regions (Kinsbourne, 1980; T. A. Salthouse, 2000). In fact, the latter occurrence has been by shown by functional neuroimaging (positron emission tomography, PET; functional magnetic resonance imaging, fMRI) for over a decade. Indeed, one of the most robust findings since the advent of functional neuroimaging is that, compared to younger adults who tend to compartmentalize functional activity during a given cognitive task, older adults tend to exhibit more diffuse activity and engage more structures bilaterally (both hemispheres). This consistent finding has been termed the HAROLD phenomenon (hemispheric asymmetry reduction in older adults) (Cabeza, 2002) and has been shown across multiple cognitive domains.

However, it is not clear whether the HAROLD phenomenon implies age-related dedifferentiation per se (Park et al., 2004). That is, it is not known whether the additional activity reflects the recruitment of more neural resources that are functionally specialized for the task being performed (which does not reflect dedifferentiation of function), or whether it reflects the incorporation of areas that are specialized in young adults but perform more general functions in older subjects (consistent with functional dedifferentiation) (Park et al., 2004; Rajah & D'Esposito, 2005). Yet another possibility is that the bilateral activation is epiphenomenal and does not contribute to dedicated neural mechanisms. Finally, it is possible that the additional activity is unwanted and detracts from performance, as was suggested by Crosson et al. (B. Crosson et al., 2003), for example, during language production.

Dedifferentiation at the neural level has been defined by some as a change in the spatial pattern of brain activation with age as a result of decreased neural specificity (Cabeza, 2002; Park et al., 2004; Voss et al., 2008; Zarahn et al., 2007) but only a few studies have explored this occurrence and the results have not been discussed as relating to the (multivariate) dedifferentiation literature. Studies that have operationally defined neural dedifferentiation in this way have quantified it by calculating the degree of spatial overlap for a given region between cognitive tasks. However, spatial overlap alone may not fully capture the nature of the phenomenon and does not fully bridge the gap between HAROLD findings and the multivariate dedifferentiation literature. What is also needed is a measure of functional overlap to show that spatial differences seen during fMRI are related to functional integration of these regions, as well. One way of looking at functional relationships is with participants' blood oxygenation level-dependent (BOLD) (Ogawa et al., 1990) responses. To our knowledge, only one study (Voss et al., 2008) has used a quantitative measure of dedifferentiation that included BOLD response. Looking at the neural specificity in the visual cortex for processing color, words, faces, and places, these authors calculated a discriminibility metric that was the average activation (percent signal change) to the preferred stimulus-localized region of interest (ROI), divided by the average standard deviation of the response amplitude for preferred and all non-preferred stimulus conditions within the preferred stimulus-localized ROI. We agree with these authors that a quantitative measure of dedifferentiation that takes into account both magnitude and variance of activation would help examine not only age-related differences, but also could potentially be used as a tool to study individual differences within an aging cohort. A metric that includes BOLD response is better able to look at functional overlap (as opposed to spatial overlap), is less sensitive to thresholding artifacts that can arise when comparing old and young

subjects, and helps account for the greater variability seen in older adults' response amplitude across time (Voss et al., 2008).

The present analysis is based on data collected from another study designed to examine the HAROLD phenomenon during category member generation (Benjamin, Cohen et al., in preparation). Here, we draw from another methodology, functional connectivity, to provide another BOLD-derived index of functional dedifferentiation. Functional connectivity is not a crisp methodological term but rather a class of analyses defined independently by different researchers and with different imaging modalities (fMRI, EEG, PET). For the present analysis, we adopt the definition provided by Rogers et al. (Rogers et al., 2007) that functional connectivity means "the quantification of the operational interactions of multiple spatially distinct brain regions that are engaged simultaneously in a task." These authors have also noted that, "while specific analytic techniques vary, a common feature of multiple fMRI assessments of connectivity is the use of correlations or covariances of activities derived from BOLD data." Correlated BOLD signal shows coherence and synchrony of activity between regions and has been interpreted as a marker of connectivity. Unlike "effective connectivity," a similar analysis, functional connectivity makes no attempt to describe or impose causality on separate regions or voxels. We believe this to be an appropriate technique to study dedifferentiation since a loss of functional specificity does not have an obvious directional component and it is not clear how to impose a priori hypotheses on the data. Previous BOLD fMRI studies of functional connectivity have looked at correlations of time-series data (Tivarus et al., 2008) and deconvolved impulse response functions. The present analysis investigates functional connectivity using the deconvolved hemodynamic response across blocked trials during category member generation.

In summary, the present investigation used a BOLD-derived measure of functional connectivity to investigate whether older adults' diffuse, HAROLD-typical activity during category member generation is consistent with previous conceptualizations of dedifferentiation of function in old age. Multivariate ("macro") analyses have shown that in old age, cognitive abilities become more highly related. We hypothesize that the present investigation will reflect this phenomenon at the neural level during a single cognitive task ("micro" level) as an increase in functional connectivity in old age.

CHAPTER 2
METHODS

Participants

Twenty-two older adults (ages 65-85, mean=71.3, SD=6.2) and twenty-two young adults (ages 18-35, mean=25.5, SD=4.5) participated and were matched for education level (young mean=16.4, young SD=2.3, older mean=16.3, older SD=3.2). For some analyses the group of older adults was subdivided by a median split for age to produce a Young-Old group (N=11, Mean=66.4, SD=0.92) and an Old-Old group (N=11, Mean=76.2, SD=5.3). In the Young group there were 10 men and 12 women. In the Young-Old group there were 4 men and 7 women. In the Old-Old group there were 9 men and 2 women.

Young adults were recruited from the University of Florida and Santa Fe College (Gainesville, FL) communities and older adults were recruited from the community at large. All participants were native English speakers and right-hand dominant, as determined by the Edinburgh Handedness Inventory (Oldfield, 1971). Potential participants were excluded if they reported a history of neurological disease, dementia or mild cognitive impairment, cardiovascular disease, uncontrolled hypertension, Diagnostic and Statistical Manual of Mental Disorders American Psychiatric Association [DSM-IV-TR], 2000) Axis I diagnosis including learning disability, attention deficit hyperactivity disorder, and substance abuse, or if they were taking prescription psychoactive medications. Participants were also extensively screened to make sure they were free of metal in their body (other than dental fillings). Potential female participants were excluded if they were pregnant or trying to become pregnant. Participants were instructed to abstain from caffeine on the day of the scan. All participants gave written informed consent in accordance with a protocol approved by the Health Center Institutional Review Board at the University of Florida and were paid US $25 as reimbursement for travel expenses.

Dementia Screen

Prior to being enrolled in the functional magnetic resonance imaging (fMRI) study, older participants were administered a standard health history questionnaire and completed brief cognitive tests to screen for dementia or Mild Cognitive Impairment-amnestic type, a precursor to pathological aging and a high-risk condition for the development of clinically probable Alzheimer's disease (Petersen et al., 2001). Individuals were excluded had they reported subjective memory complaints, scored below 27 out of 30 on the Mini-Mental State Exam (MMSE) (Folstein et al., 1975)or obtained a total recall score (trials 1–3) of less than 15 on the Hopkins Verbal Learning Test (HVLT) (Shapiro et al., 1999), a test of auditory-verbal working memory. No subjects were excluded for any of these reasons.

Assessment of Language

Outside of the scanner, all participants completed the category (animal) fluency subtest from the Delis-Kaplan Executive Functioning System (D-KEFS) (Delis, 2001) and responses were clustered into four 15-second intervals. Older participants were additionally administered the Boston Naming Test (Kaplan, 1983) to assess confrontation naming.

Functional Magnetic Resonance Imaging (fMRI) Category Member Generation Task

During fMRI, participants covertly (i.e. silently) generated members of the given category for 17 seconds (10 TR). Covert generation was determined to be the best methodology due to the many difficulties associated with overt naming during fMRI trials (B. Crosson et al., 2007), including movement and respiratory artifact, and because covert generation was known to elicit cortical as well as cortical activity (Crosson et al. 2003). Category members were presented visually and aurally at the same time with a stop cue at the end of the 17 seconds. Sixteen total categories (order counterbalanced) were presented across 2 fMRI echo-planar imaging (EPI) runs in a blocked design format with 10.2, 11.9, and 15.3 seconds intervals between active

blocks, during which participants fixated on a cross, which served as a baseline of activity. Examples of categories includes: birds, beverages, lunch meats, occupations, ocean animals.

Image Acquisition

Images were acquired on a Siemens Allegra 3.0 Tesla head-only scanner with the standard quadrature radio frequency head coil. Functional images were obtained with a 1-shot gradient echo planar imaging (EPI) scan: 240mm field of view (FOV), 64x64 matrix (3.75 x 3.75 in-plane resolution), repetition time (TR)=1700ms, echo time (TE)=25ms, flip angle (FA)=70°. Thirty-two 5mm axial slices covering the whole brain were acquired. A high-resolution T1-weighed 3D rapid acquisition gradient echo (MP-RAGE)scan (TE=4.13ms, TR=2000ms; FOV=240mm; FA=8°; matrix size=256x192mml 128 1.3mm slices) was obtained to provide anatomic reference. Head motion was minimized using foam padding.

Data Analysis

fMRI data were analyzed and overlaid on structural images with the Analysis of Functional Neuroimaging (AFNI) software package from the National Institutes of Health (Cox, 1996). The first 6 images of the functional runs were discarded to ensure stability of the imaging matrix. Time series images were spatially registered in three-dimensional space to minimize the effects of head motion. The two imaging runs were concatenated into a single time series. Two participants were omitted from analysis, one for benign cortical calcifications and a second for use of a prescription calcium ion blocker, leaving the 22 subjects per group (described above).

For each voxel of each subject, the obtained fMRI intensity time-series was modeled with AFNI's 3dDeconvolution program as the convolution of the experimental stimulus vector and the estimated best-fit twelve-lag impulse response, allowing the hemodynamic response (HDR) to return to baseline. Subject values were scaled to reflect Z scores. The mean value of the deconvolved impulse response function (mean-IRF) was the dependent variable for analyses and

was calculated by adding the deconvolved image intensity at each deconvolved time point of the impulse response. The T1-weighted anatomic images and the mean-IRF functional activation maps were warped to the coordinates of the co-planar stereotactic atlas of Talairach and Tornoux (Talairach, 1988) and resampled at a $1mm^3$ resolution. Functional images were then spatially smoothed with a Gaussian kernel of 4mm full-width at half-maximum.

Within-group comparisons of the area under the curve (AUC) during covert category member generation against zero were conducted with voxel-wise t-tests for young and older adults. Between-group comparisons were made with voxel-wise t-tests, as well. A cluster threshholding technique was implemented to determine which areas of activation on the t-maps were significant by threshholding at a single-voxel p-value less than 0.0001 for within-subject data and less than 0.005 for between-subject data. The cluster size was predetermined as a region of at least 250 contiguous voxels (i.e. $250mm^3$).

Functional Connectivity Analysis

(1) Masks of each active region identified from the clustered t-maps (generated from group data) were generated to produce one set of masks of active regions for the young group and a second set for the old group. (2) These masks were then applied to the individual subjects within each respective group and a mean-area under the curve value was extracted for each (group-identified) region for each subject. (3) For each age group, subject values for each active region were correlated (Pearson r) with all other regions for all group members, resulting in a matrix of intercorrelations among active regions for each group. (4)Correlations with an associated alpha less than 0.01 were isolated and patterns of functional connectivity were identified.

CHAPTER 3
RESULTS

For a more comprehensive report of the results, the reader is referred to Benjamin, Cohen et al. (in preparation).

Behavioral Results

On the Delis-Kaplan Executive Function System (DKEFS) animal fluency test, Young participants produced a mean of 8.2 category members in the first 15 seconds (SD=1.6) and 23.5 words at 60 seconds (SD=5.6). Old (Young-Old + Old-Old) participants generated a mean of 9.0 words in the first 15 seconds and 20.8 words at 60 seconds (SD=4.0). Old and Young participants did not differ on the number of category members produced at 15 seconds (mean difference=-.82, $t(42)=-1.78$, $p<.082$) or at 60 seconds (mean difference=2.64, $t(42)=1.8$, $p<.079$).

When the Old group was subdivided into Young-Old and Old-Old, the Young-Old group generated 8.36 (SD=1.2) category members at 15 seconds and 22.2 (SD=3.9) at 60 seconds. The Old-Old group generated 9.63 (SD=1.4) category members at 15 seconds and 19.4 (SD=3.7) at 60 seconds. Their performances were significantly different at 15 seconds (mean difference=-1.27, $t(20)=-2.25$, $p<.036$) with the Old-Old group producing significantly more words than the Young-Old group, but there was no group difference at 60 seconds (mean difference=2.27, $t(20)=1.7$, $p<.112$). The Young-Old group did not differ from the Young group at 15 seconds (mean difference=-.18, $t(31)=-.33$, $p<.741$) or at 60 seconds (mean difference=1.27, $t(31)=.67$, $p<.459$). The Old-Old group, however, did produce significantly more words than the Young group at 15 seconds (mean difference=1.45, $t(31)=-2.53$, $p<.016$) and significantly fewer words at 60 seconds (mean difference=4.0, $t(31)=2.145$, $p<.04$).

Within the Old group, Young-Old and Old-Old participants did not differ in their level of education or on their performances on the BNT or HVLT. They were significantly different with

respect to their age (discussed earlier, section 2.1) and in the sex composition of the groups ($t(20)=-2.3$, $p<.03$). The Young-Old group had 4 males and 7 females, while the Old-Old group had 9 males and 2 females.

Functional Magnetic Resonance Imaging (fMRI) Results

Within-Subject fMRI Results

Young participants demonstrated 7 active regions at the level of thresholding described previously ($t=4.7$, $p<.0001$, 250μl, 1.8mm) (Table 3-1), including two clusters in the left middle frontal gyrus, one cluster in the left pre-central gyrus, one in the left caudate body, one in the left pre-supplementary motor area (pre-SMA), and one in the right cerebellum. The pre-SMA was defined for each age group as the portion of Brodmann's Area (BA) 6 anterior to a coronal plane passing through the anterior commissure of the Talairached T1 image. This line has been shown to be a good landmark for distinguishing between the two regions (Picard & Strick, 1996). The SMA was defined as the region within BA 6 posterior to this line.

Old (Young-Old + Old-Old) participants demonstrated 6 large clusters of strong activity at the selected level of thresholding (Table 3-1). Though the older adults demonstrated fewer clusters at the same threshold, the clusters tended to be larger than the ones shown by young adults and traversed multiple anatomic regions. A more stringent threshold was not used in order to maintain equivalency with the Young adults and because at higher levels of activity (i.e. greater than $t=4.7$, $p<.0001$), right cortical and subcortical activity becomes less prominent and these were areas of special interest. Some of the demonstrated clusters were manually divided based on anatomical boundaries (for example, SMA and pre-SMA, described previously) or based on boundaries that emerged at higher thresholds. These divisions resulted in 16 anatomically distinct regions. Additionally, though the Older participants were subdivided into Young-Old and Old-Old in analyses of BOLD response, they were kept together for the

identification of clusters in order to retain maximum statistical power and equivalency with the group of Young participants. Active regions include the left middle frontal gyrus, left inferior frontal gyrus, left pre-central gyrus, left insula, pre-SMA bilaterally, thalamus bilaterally, caudate body bilaterally, and right SMA.

Between-Subjects fMRI Results

When Old (all 22) participants' mean IRF was contrasted against Young participants ($t=2.91, p<.005$, 250ul, 1.8mm), 10 areas of difference were revealed, all of which demonstrated greater activity in Older participants (Table 3-2). These areas included the left middle frontal gyrus, left inferior frontal gyrus, pre-SMA bilaterally, putamen bilaterally, right thalamus, right Broca's homologue (BA 47), and right SMA.

When Old-Old (n=11) participants were contrasted with Young-Old (n=11) participants ($t=2.91$, $p<.005$, 250ul, 1.8mm), 9 areas of differences were revealed (Table 3-2), all of which demonstrated greater activity in the Old-Old participants. Results showed that Old-Old adults showed stronger activity than Young-Old adults in the left middle frontal gyrus, left inferior frontal gyrus, left superior frontal gyrus, lentiform nuclei bilaterally, left thalamus, right cingulate cortex, as well as the right precuneus. An area of activation was also shown in the right brain stem.

Functional Connectivity Results

Young Participants

When the mean activation of all voxels within each cluster (within-subjects; 7 clusters total) was correlated with the average activation from all other within-subjects clusters, a matrix of 21 possible correlations was produced (Figure 3-1). Of these 21 possible correlations, the group of Young participants demonstrated significant ($p<.01$) correlations for 13 (62%) of them. The left insula was not correlated with any other cluster except the right cerebellum, the left

middle frontal gyrus was not correlated with the left pre-SMA or the left pre-central gyrus. The left pre-central gyrus also failed to show significant correlation with the right cerebellum. All other correlations were significant.

Young-Old Participants

Of the 120 possible correlations between the 16 active regions; within-subjects) of Older participants, only 8 (6.7%) relationships were found to be significant in the Young-Old group (Figure 3-2). Five of these were areas correlating with left and right pre-SMA clusters, one between the left post-central gyrus and the left superior temporal gyrus, one between the left and right caudate, and one between the left and right thalamus.

Old-Old Participants

Of the 120 possible intercorrelations between active areas for the Older participants, the Old-Old participants demonstrated 89 (74%) significant relationships (Figure 3-3). Notably, almost all (24) of the nonsignificant correlations were with the left and right thalamus.

Table 3-1. Within-subject activity against baseline

Brain areas showing activity at or above t=4.78 (p<.0001) and 250mm^3 (contiguous voxels)

Anatomical Location	BA/Subregion	Volume (mm^3)	Peak Intensity (x, y, z)
YOUNG ADULTS			
L Premotor	L Pre-SMA/SMA	2619	40, 0, 35
L Middle Frontal Gyrus	L (lateral) BA 6	765	46, -1, 27
	L BA 9	1140	37, 21, 24
L Motor	L BA 4	462	39, 6, 50
L Caudate		790	14, -6, 13
L Insula	L BA 13/14	380	27, -20, 7
R Cerebellum	R Culmen	818	-35, 55, -26
OLDER (all 22) ADULTS			
L PCG, MFG, IFG*	L BA 6,9, 45,46	8701	40, 0, 35
L/R pre-SMA/ SMA**	L/R BA 6	5478	3, 2, 55
L Caudate, Lentiform, Thal*		1680	19, -5, 9
R Caudate, Lentiform, Thal*		905	-17, -9, 8
L Precuneus	L BA 19	422	27, 70, 40
L MFG (superior)	L BA 6	258	25, -5, 58

L=left; R=right; IFG=inferior frontal gyrus MFG=middle frontal gyrus PCG=precentral gyrus SMA=supplementary motor area

* Older adults demonstrated very strong activity. Clusters are reported here at the same threshold as young adults but the clusters marked with an (*) were manually divided based on anatomical divisions and boundaries that emerged at higher levels of thresholding (not shown). The manually divided clusters are the ones used in the dedifferentiation analysis.

**SMA and pre-SMA were activated in both hemispheres. Because these areas demonstrated such strong activation, and because the SMA/pre-SMA are medial structures and drain into the same sinus(FACT CHECK), the activation seen in both hemispheres was combined into one large cluster at this threshold and were manually isolated.

Table 3-2. Between-subject activity

Brain areas showing activity at or above t=3.15 (p<.005) and 250mm^3 (contiguous voxels)

Anatomical Location	BA/Subregion	Volume (mm^3)	Peak Intensity (x, y, z)
OLDER(n=22) vs YOUNG(n=22)			
L MFG		631	
L Middle Frontal Gyrus	BA 10, 46	606	
L Inferior Frontl Gyrus	BA 47	308	
L pre-SMA/SMA	BA 6	786	
L Superior Temporal Gyrus	BA 22	290	
L Lentiform Nucleus		1826	22, 4, 0
R Middle Frontal Gyrus		771	
R Pre-Motor	BA 6 (lat)	1043	-46, 0, 26
R Lentiform Nucleus		1992	-26, -12, 5
R Ventral Thalamus		2269	-6, 7, 12
OLD-OLD(11) vs YOUNG-OLD(11)			
L Inferior Frontal Gyrus	L BA 4	284	34, 16, -6
L Middle Frontal Gyrus	L BA 46		
L Middle Frontal Gyrus	L BA 47		
L Superior Frontal Gyrus	L BA 6		
L Lentiform nucleus		584	32, 6, 2
L Subthalamic Nucleus		644	10, 9, 1
R Lentiform Nucleus		656	-18, 2, -2
R Brainstem		339	-6, 19, -26
R Cerebellum	R Precuneus	660	-2, 36, 47

Young Adults (n=22) 13 / 21 at p<.01							
Left Middle Frontal Gyrus (lat)	1						
Left Middle Frontal Gyrus (med)	0.710 0.000	1					
Left Pre Central Gyrus	0.705 0.000	0.469 0.027	1				
Left Insula	0.496 0.019	0.435 0.043	0.258 0.246	1			
Left Caudate	0.653 0.001	0.587 0.004	0.638 0.001	0.377 0.083	1		
Left pre-SMA	0.634 0.002	0.447 0.037	0.544 0.009	0.487 0.022	0.806 0.000	1	
Right Cerebellum	0.673 0.001	0.689 0.000	0.365 0.094	0.643 0.001	0.604 0.003	0.632 0.002	1
	L lateral MFG	**L MFG**	**L pre-central Gyrus**	**L Insula**	**L Caudate**	**Left preSMA**	**Right Cerebellum**

Figure 3-1. Young adults against baseline.

Young-Old Adults 8 / 120 at p<.01															
L_superior parietal	1														
L pre central gyrus	0.482 0.133	1													
L Middle Frontal Gyrus	0.260 0.439	0.527 0.098													
L Inferior Frontal Gyrus	0.060 0.862	0.320 0.337	0.274 0.415	1											
L Insula	0.502 0.116	.669(*) 0.024	0.390 0.235	.724(*) 0.012	1										
L Inferior Frontal Gyrus (anterior)	-0.042 0.903	0.429 0.188	0.433 0.183	.604(*) 0.049	0.356 0.262	1									
L Post Central Gyrus	.751(**) 0.008	0.556 0.076	0.247 0.465	0.082 0.811	0.322 0.334	0.082 0.810	1								
L Superior Frontal Gyrus	0.158 0.643	-0.129 0.704	0.257 0.445	0.227 0.502	-0.039 0.910	0.012 0.973	0.273 0.416	1							
L pre-Supplementary Motor Area	0.407 0.214	.656(*) 0.028	.678(*) 0.022	0.574 0.065	0.545 0.083	0.525 0.098	0.339 0.307	0.248 0.462	1						
L pre-Supplementary Motor Area #2	0.449 0.166	.883(**) 0.000	0.524 0.098	0.452 0.162	.777(**) 0.005	0.216 0.523	0.574 0.065	-0.035 0.918	.610(*) 0.046	1					
L Caudate	0.180 0.596	0.110 0.748	-0.076 0.824	0.558 0.074	0.426 0.192	0.085 0.804	0.383 0.245	.615(*) 0.044	0.107 0.753	0.290 0.387	1				
L Thalamus	0.332 0.318	0.346 0.297	-0.080 0.816	0.092 0.788	0.476 0.138	-0.440 0.176	0.455 0.160	0.053 0.877	-0.047 0.890	.624(*) 0.040	0.558 0.074	1			
R Thalamus	0.499 0.118	0.391 0.235	-0.117 0.733	0.096 0.780	0.526 0.097	-0.291 0.384	.623(*) 0.041	-0.089 0.795	-0.062 0.857	.616(*) 0.044	0.494 0.123	.921(**) 0.000	1		
R Caudate	0.183 0.591	0.474 0.141	0.141 0.680	0.465 0.150	0.509 0.110	0.152 0.656	0.453 0.162	0.521 0.101	0.257 0.445	0.591 0.056	.848(**) 0.001	.656(*) 0.028	0.545 0.083	1	
R pre-SMA	.692(*) 0.018	.737(**) 0.010	0.346 0.297	0.430 0.187	.658(*) 0.028	0.187 0.582	.640(*) 0.034	-0.090 0.793	.694(*) 0.018	.771(**) 0.005	0.101 0.768	0.321 0.335	0.422 0.196	0.214 0.528	1
R SMA	.602(*) 0.050	0.567 0.069	0.130 0.703	0.185 0.585	0.514 0.106	-0.246 0.467	.643(*) 0.033	0.196 0.563	0.357 0.282	.740(**) 0.009	0.338 0.310	.701(*) 0.016	.673(*) 0.023	0.568 0.066	.703(*) 0.016
	L Sup Par	**L pre-CG**	**L MFG**	**L IFG**	**L Insula**	**L IFG (ant)**	**L post-CG**	**L sup front G**	**L pre-SMA**	**L preSMA2**	**L Caudate**	**L thalamus**	**R thalamus**	**R caudate**	**R preSMA**	**R SMA**

Figure 3-2 Young-old adults against baseline.

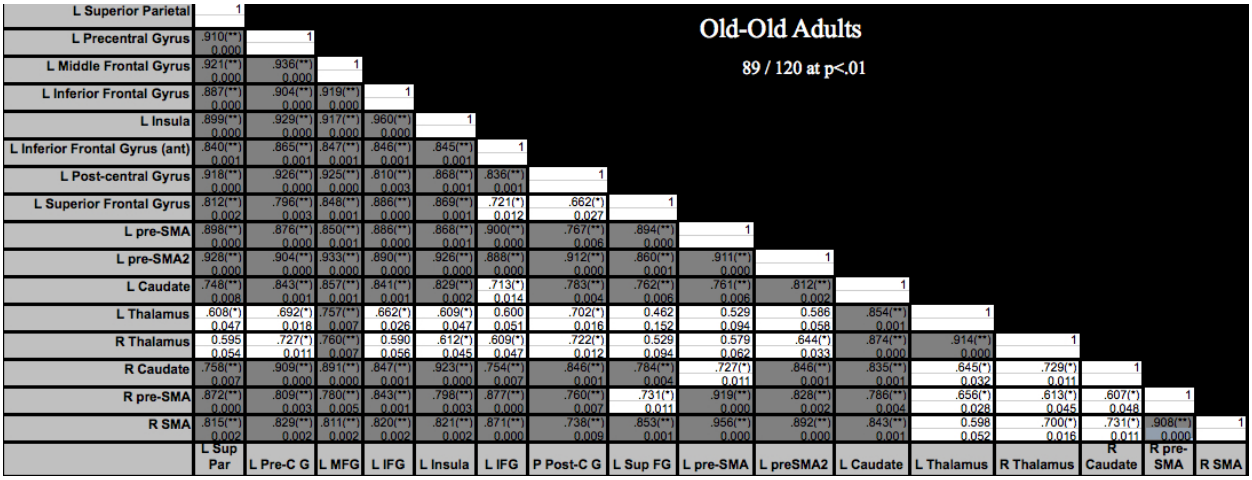

Figure 3-3 Old-old adults against baseline.

CHAPTER 4
DISCUSSION

Consistent with previous investigations of HAROLD (hemispheric asymmetry reduction in older adults), Older adults' activity during this task was observed to be more diffuse than Young adults. That is, older adults showed stronger activity and in more areas than the young adults (including right hemisphere structures) and engaged the same structures as young adults but with less precision. The Young adults did not show greater activity than older adults in any area. If the groups differed in the number of category members generated, these results could have been explained by performance differences. However, the groups of Young and (all) Older adults did not differ on the test of spoken category member generation performed outside of the scanner at 15 seconds, so we believe that their covert generation in the scanner was most likely equivalent. It is therefore believed that the observed results reflect true age-related differences and are not due to more superficial explanations. Also, Old-Old adults demonstrated 9 areas of greater activity than Young-Old adults, which suggests that the HAROLD phenomenon is progressive with age. That is, the phenomenon is noticeable when comparing 66-year-olds to 25-year-olds, and also when comparing 76-year-olds to 66-year-olds.

The consideration of functional connectivity data provides interesting insight into the HAROLD occurrence. Young adults display correlations (connections) that are consistent with the structures indicated by Crosson et al. (B. Crosson et al., 2003) to be involved in the task, including connections between the left pre-SMA, caudate, and frontal cortical regions. The most interesting results emerge when the Young-Old adults are contrasted with the Old-Old adults. Despite showing significant activity in 16 regions, the Young-Old participants only demonstrated 8 significant connections between them (out of a possible 120). Old-Old adults, however, showed 89 significant connections between these same regions. This suggests that spatial

changes in activation in old age (e.g. HAROLD) do not necessarily mean functional changes. That is, in Old-Old adults (mean age=76), the diffuse activation does appear to imply functional dedifferentiation. Young-Old adults, however (mean age=66), seem to show HAROLD-typical activity without functionally integrating active regions.

Based on the specific patterns of functional connectivity in the different groups, we propose three possible explanations of the findings. The first explanation describes the findings in the context of the brain compensating for age-related losses, like what has been previously described with HAROLD findings (Cabeza, 2002). The second involves age-specific deterioration of basal ganglia pathways. The third way reflects a lack of selective engagement of cortical structures from the thalamus (Nadeau & Crosson, 1997).

Compensation

The most commonly-endorsed explanation of HAROLD activity is that the diffuse activation reflects the brain trying to recruit more neural resources to compensate for age-related deterioration. It is possible that the results from the Young-Old group show an early stage in the recruitment of more resources. The neurons of the newly-recruited areas are firing (and therefore show significant associated BOLD signal) but their contribution is not yet integrated into functional networks (as inferred from a lack of correlations). This is supported by the behavioral data that showed that Old-Old adults generated significantly more items than Young-Old adults in the first 15 seconds of the DKEFS semantic fluency task, suggesting that they have more successfully compensated for age-related declines than the Young-Old adults. It is also interesting to note that in the Young-Old adults, 6 of their 8 significant connections are between homologous or nearly-homologous regions: left and right caudate, left and right thalamus, left and right pre-SMA. This suggests that the first connections that are made in the process of compensation are the ones between homologous regions.

Age-Specific Deterioration of Basal Ganglia Circuitry

A second explanation of the results involves unique basal ganglia deterioration associated with each age group. This discussion requires a brief orientation to the functional neuroanatomy of category member generation, previously explored by Crosson et al. (B. Crosson et al., 2003; B. Crosson, Benjamin, M., and Levy, I, 2007) and others. These authors modified previous ideas of basal ganglia functioning (Alexander et al., 1986; Mink, 1996; Penney & Young, 1986; Strick, 1995) and applied them to language tasks. Their model proposed that the basal ganglia are employed to help refine cortical activation so that the neural representations of individual lexical and semantic items (e.g. category members) are rapidly enhanced and then suppressed in favor of the next produced item. Given a category (e.g. “birds”), the signal to noise ratio (SNR) is refined for a chosen response (e.g. “birds”) by enhancing the unique signal associated with that item (e.g. “robin”) while suppressing related and competing items (e.g. “blue jay”). The basal ganglia are then also recruited to suppress “robin” in favor of the next item. Thus, the basal ganglia help improve the speed and accuracy of response, while also serving as a “clutch” in the transition between items.

Figure 4-1 describes the relationship among structures in three subcortical circuits. The “direct” pathway is believed to enhance the signal of the desired output and involves projections from the pre-SMA to a dedicated neostriatal component, and then to the medial globus pallidus (GPi). Striatal spiny output neurons that participate in the direct loop cycle through two states: a hyperpolarized “down” state and a less polarized “up” state that prepares the neurons for an action potential. Because excitatory cortical inputs terminate rather diffusely on striatal neurons, it takes a strong and coordinated cortical input to excite those neurons into the “up” state. However, the transition to “up” state is facilitated by the activation of dopamine D1 receptors that are innervated with dopamine from the substantia nigra pars compacta (SNpc). Thus, active

D1 receptors “may facilitate selected actions or cognitions through prolonging the activity supporting them” (B. Crosson, Benjamin, M., and Levy, I, 2007).

Competing responses to the selected output are attenuated by the “indirect” loop which involves projections from the striatum to the lateral globus pallidus (GPL) to the subthalamic nucleus (STN), and then to the medial globus pallidus. Input from the direct and indirect pathways summate at the GPm, which then determines the degree of suppression that the GPm exerts on the thalamus. The greater the activity of the GPm, the more suppression is imposed on the thalamus. The indirect loop is believed to be mediated by dopamine D2 receptors, though the exact mechanics are far less understood than for the direct pathway.

The role of the basal ganglia during category member generation is further complicated by the presence of a third loop, the “hyperdirect” loop (Nambu et al., 2000) that projects excitatory information directly from the pre-SMA to the STN, which then causes the GPm to inhibit the thalamus. These three loops work together to form a temporal sequence of suppress-enhance-suppress. Nambu et al. showed that following excitation of motor cortices, the GPm experienced three waves of input. The first (8 ms after stimulation) was excitatory and was believed to be the hyperdirect pathway. By strongly activating the GPm, the thalamus is strongly inhibited and it is speculated that this may serve to reset the basal ganglia circuitry in preparation for changing to a new activity (Nambu et al., 2002). The second wave (22 ms) was inhibitory on the GPm and was believed to be the direct pathway (enhancing desired output). Finally, the third wave (30 ms) was excitatory and was believed to be the indirect pathway (suppress competing output). These three pathways and their temporal pattern will help interpret the connectivity changes observed in the results of the present investigation.

It is possible that the different patterns of functional connectivity seen in Young-Old and Old-Old adults reflect age-specific losses of the direct and indirect pathways. A loss of the efficacy of the direct (enhance) pathway might account for the lack of functional recruitment of active regions seen in the Young-Old group, while a loss of the efficacy of the indirect pathway might cause the widespread functional engagement of regions seen in Old-Old adults. That is, they are no longer able to suppress unwanted "noise." It is already known that aging results in a loss of basal ganglia dopamine receptors, both D1 (Wang et al., 1998) and D2 (Vernaleken et al., 2007). However, it is not know at what rate or during which critical periods these declines occur. Perhaps the results of the present investigation first reflect a loss of D1 receptors that mediate the direct pathway (age 66), followed by a loss of D2 receptors that mediate the indirect pathway (age 76).

A third possibility is that the widespread functional connectivity seen in the Old-Old group reflects an inability to selectively engage task-related neural networks. Nadeau & Crosson (1997) discussed the possibility that dysfunction of the pulvinar and lateral posterior nuclei of the thalamus may disrupt the ability of the thalamus to enlist specific neural nets to complete a task without engaging unnecessary resources. Perhaps the relative lack of connectivity with the thalamus in the Old-Old group is indicative of thalamic dysfunction and the widespread functional connectivity of all other regions results from the thalamus' inability to confine neural activity to critical networks only. Though conceptually similar to the previous possibility, a decreased ability to selectively engage neural nets represents a recruiting deficiency, whereas the previous possibility represents an impaired ability to refine the output of already-engaged structures.

There are several important limitations of the investigation that should not be overlooked. First, it is not known to what degree these findings will generalize to cognitive tasks other than category member generation or to groups of a lower education level. Second, as with any cross-sectional analysis of dedifferentiation comes the assumption that between-person differences will be reflective of intraindividual changes across time. Though this assumption is an accepted one, further analysis with longitudinal analyses is necessary (Sims, 2008).

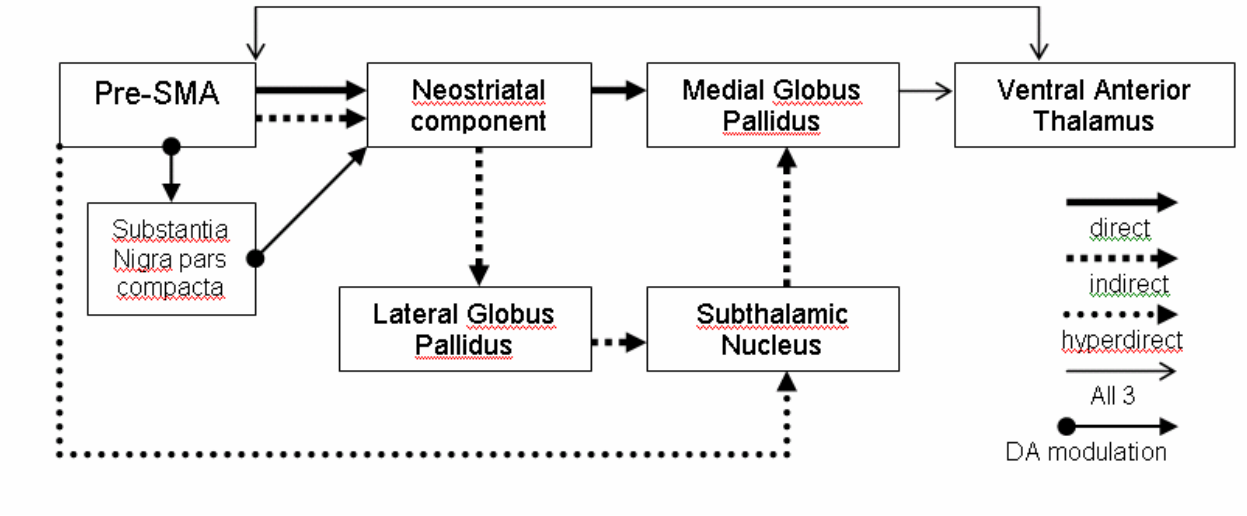

Figure 4-1. Direct, indirect, and hyperdirect loops of the basal ganglia.

CHAPTER 5
CONCLUSION

Results show that patterns typical of the HAROLD phenomenon (hemispheric asymmetry reduction in older adults) can be informed by analyses of the functional connectivity of active regions and that using the mean (blood oxygenation level dependent; BOLD) impulse response function is one method of doing so. Specifically, functional connectivity analysis has shown that in Old-Old adults (mean age=76), HAROLD-typical activation does appear to reflect dedifferentiation of function, as supported by the functional integration of (almost) all active regions. However, results from the Young-Old group (mean age=66) suggest that there appears to be a preceding stage whereby many neuroanatomical regions are active but not functionally integrated. Perhaps this reflects an early stage of a compensatory mechanism that is recruiting more resources to account for age-related decline. Alternatively, the results might be explained as a loss of D1 receptors in the Young-Old group, followed by a loss of D2 receptors in the Old-Old group. Finally, perhaps the results reflect an inability of the thalamus to selectively engage networks needed for the task.

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BIOGRAPHICAL SKETCH

Matthew L. Cohen graduated magna cum laude from the University of Delaware (UD) in 2007 with an honors Bachelor of Arts degree with distinction in psychology and with minors in biology and Spanish. His research at UD focused on the interrelationship between young children's theory-of-mind and language acquisition. He began his graduate studies in clinical psychology, specializing in clinical neuropsychology at the University of Florida in the Fall of 2007 and was awarded an Alumni Fellowship. He has been mentored by Dr. Bruce Crosson and his research has used neuroimaging to study subcortical contributions to language production both in healthy older adults and clinical populations. He obtained his M.S. degree in May, 2009 and is pursuing a Ph.D.