CORTICAL-SUBCORTICAL FUNCTIONS IN VERB AND NOUN GENERATION

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Neuroimaging studies of word generation to date have focused primarily on phonemic fluency and category-member generation for objects. Given that behavioral studies of verbal fluency have found that verbal fluency for actions may strongly implicate frontal-striatal neuroanatomical systems and that imaging studies in healthy aging have implicated bilateral lateral frontal activity in old adults but not young adults, the current study sought to compare noun and verb generation in old and young healthy adults using functional magnetic resonance imaging (fMRI). Fifteen old adults (age range: 71 to 89 years) and 15 young adults (age range: 18 to 32 years) were compared for the current fMRI study of covert word generation. Subjects were presented with blocks of either three nouns or three verbs and were asked to generate silently an item semantically related to the stimulus within the same grammatical class for each of the three stimuli as they were presented. In whole-brain between-group analyses, significant group differences were found in the right precentral gyrus for the noun condition and in the right inferior frontal sulcus for the verb condition, with old subjects demonstrating greater activity in these cortical regions. Significant group differences were also found for both generation conditions in left posterior regions typically

associated with semantic processing (i.e., left angular gyrus), with old subjects demonstrating greater activity in the angular gyrus in both generation conditions. In addition, a priori anatomy-based ROIs showed significant between-group differences over the fMRI time course for the subthalamic nucleus (STN) bilaterally and left caudate nucleus during noun generation, with greater STN activity found in old adults but greater left caudate activity in young participants. Within-group whole-brain analyses indicated significant bilateral lateral frontal, medial frontal, and subcortical activity for both age groups during both types of word generation, implicating a bilateral cortical-subcortical network for the current noun and verb generation task regardless of age. Findings from the study suggest that the current paradigm is capable of eliciting an extensive cortical-subcortical network for evaluating differences in language production in the healthy aging population and may be applicable for patient populations with frontal-striatal involvement.

CHAPTER 1
INTRODUCTION

The current project studied aging differences in language production via function magnetic resonance imaging (fMRI) using a noun and verb generation paradigm. While the current study did not propose to examine performance in clinical populations, the impetus behind the current paradigm was a clinical one. The longer-term objective of this study was to develop a functional neuroimaging language paradigm with adequate sensitivity for detecting subcortical activation during language tasks that can be implemented using fMRI in clinical populations with known neuropathology affecting frontal-striatal systems. Chapter 2 will first summarize the structures and functions of the basal ganglia. An outline of relevant functional imaging studies of language is provided in Chapter 3. Research studies of neurological patient populations pertinent to the current study are discussed in Chapter 4. Hypotheses for the current study are presented in Chapter 5. Methodology for the current study is outlined in Chapter 6. The results for the fMRI noun and verb generation task are presented in Chapter 7, with discussion of study findings following in Chapter 8.

CHAPTER 2
BASAL GANGLIA ANATOMY, FRONTAL-STRIATAL CIRCUITRY, AND THE ROLE OF THE BASAL GANGLIA IN COGNITION

The basal ganglia are a set of subcortical anatomical structures that have important neuroregulatory implications for motor and cognition functions. In order to understand the functions of the basal ganglia, one needs to have a clear understanding of their anatomy. The following text and Figure 8-1 provide an introduction to basal ganglia anatomy and circuitry and the basal ganglia's role in neuroregulatory functions.

General circuitry and anatomy of the basal ganglia

Anatomical structures of the basal ganglia. The basal ganglia are a set of subcortical anatomical structures with neuroregulatory implications for cognitive and motor functions. The neurons of the basal ganglia themselves do not hold task-specific information, but instead function in conjunction with other cortical and subcortical structures via cortical-striatal-pallidal-thalamo-cortical circuits to enhance target behaviors or to suppress competing behaviors (Mink, 1996; Nambu, Tokuno, & Takada, 2002). The basal ganglia consist of the striatum, globus pallidus, subthalamic nucleus (STN), and substantia nigra (SN). The striatum can be further delineated anatomically into the *neostriatum* consisting of the caudate nucleus and putamen and the *archistriatum* consisting of the nucleus accumbens and olfactory tubercle. The globus pallidus can also be divided into components consisting of the internal globus pallidus (GPi) and external globus pallidus (GPe); a ventral pallidum is connected to the archistriatum.

Neurotransmission of the basal ganglia. In general, the basal ganglia receive cortical input via excitatory glutaminergic neurotransmission, and the output of the basal ganglia goes back to the cortex by means of excitatory glutaminergic neurotransmission

from the thalamus. STN neurotransmission is excitatory via glutamate to the medial globus pallidus. Neurotransmission from the substantia nigra pars compacta (SNpc), which projects to the neostriatum, can be either inhibitory or excitatory via dopamine. Neurotransmission from the striatum and globus pallidus to target structures is inhibitory via gamma amino butyric acid (GABA). Striatal afferents are the cortex or SNpc, and striatal efferents are the segments of the globus pallidus. The major afferent to the globus pallidus is the striatum, and the target structures of the globus pallidus efferents are the thalamic nuclei. Inhibition of the thalamus via the globus pallidus is dependent on input from the striatum. For example, if there is more input from the striatum, this will result in greater inhibition of the globus pallidus. This pallidal inhibition will in turn will result in less inhibition of the thalamus, resulting in greater thalamic excitatory output to the cortex.

Organization of frontal-striatal circuitry

Frontal-striatal parallel circuits. While the aforementioned information provides a basic schema for the anatomy of the basal ganglia structures, one must understand the concept of parallel functioning in frontal-striatal circuitry in order to understand the neuroregulatory role of the basal ganglia. The basic understanding of parallel cortical-subcortical circuitry is that the cortex forms closed loop circuits with the basal ganglia and thalamus (Alexander, Delong, & Strick, 1986; Middleton & Strick, 2000a, 2000b). There is somatotopic organization within these frontal-striatal circuits, in that specific cortical areas project to specific portions of the STN, striatum, and globus pallidus, which then in turn project to specific thalamic nuclei and then back to the cortex from which the cortical projection originated. Alexander, Delong, and Strick (1986) initially described five cortical-subcortical closed-loop parallel circuits originating from and

projecting to areas within the frontal lobes. These five loops consist of the supplementary motor area (SMA), the frontal eye fields (FEF), the dorsolateral prefrontal cortex (DLPFC), orbitofrontal cortex (OFC), and anterior cingulate cortex (ACC). Middleton and Strick (2000b) further delineated these circuits, and Figure 8-1 provides an example of one such cortical-subcortical loop using the pre-supplementary motor area (pre-SMA) as an example.

Temporal aspects of frontal-striatal circuits. In addition to the structural organization, there are temporal aspects of the basal ganglia circuitry to consider with regards to the neuroregulatory role of the basal ganglia. Traditionally, frontal-striatal circuits have been characterized in terms of two pathways--the direct and indirect pathways. The direct pathway is thought to enhance selected behaviors, whereas the indirect pathway is thought to suppress competing behaviors (Mink, 1996). In the direct pathway, the cortical projection to the striatum is excitatory via glutamate. Striatal projections are inhibitory via GABA and go to the GPi. GPi's projections are to the thalamus and are also inhibitory via GABA. The thalamus's projection is excitatory via glutamate back to the cortex. In the indirect pathway, the cortex also projects to the striatum using the excitatory neurotransmitter glutamate. However, the striatum then projects to the GPe using GABA. The output from the GPe then goes to STN and uses the inhibitory neurotransmitter GABA. The output of the STN is excitatory to the GPi using glutamate. GPi then projects to the thalamus and is inhibitory using the inhibitory neurotransmitter GABA. Lastly, the thalamus's projection is excitatory via glutamatergic projections back to the cortex. Mink (1996) outlined in great detail the functions of these

structures and circuits and proposed a theoretical center-surround model of the excitatory and inhibitory influences of the direct and indirect pathways, respectively.

In addition to the direct and indirect pathways, Nambu and colleagues (2000, 2002) have more recently described the role of the STN and a third pathway, termed the hyperdirect pathway. This hyperdirect pathway bypasses the striatum and is directed from the cortex directly to the STN, which then projects to the GPi. As previously outlined, the STN also participates in the indirect pathway via excitation to the GPi. However, in the hyperdirect pathway, cortical input bypasses the striatum altogether, projecting directly to the STN which then projects to the GPi. Nambu and colleagues (2000) suggest that output resulting from the hyperdirect cortico-STN-pallidal-thalamo-cortical loop occurs more quickly than that exhibited by the direct and indirect pathways. The hyperdirect pathway is thus thought to participate in early suppression or "resetting" of behavior prior to the enhancement and suppression actions of the direct and indirect pathways, respectively. The cortical-subcortical loop displayed in Figure 8-1 provides an overview of the projections for the hyperdirect, direct, and indirect pathways.

Implications for the basal ganglia in language

Knowledge of the aforementioned basal ganglia circuitry helps to provide a framework for conceptualizing the implications of the basal ganglia in language functions. As previously mentioned, the role of the basal ganglia involves neuroregulation within cortical-subcortical networks. One influential functional neuroimaging study examining the role of the basal ganglia in language functions was a study done by Crosson and colleagues (2003) investigating the contributions of the left and right basal ganglia and frontal activation during word generation in young adults. Their study involved examining three types of generation stimuli [phonological

(nonsense syllable), lexical (rhyming), and semantic (category member)], and the findings of the latter two paradigms are the most pertinent to the current research proposal. During lexical retrieval (rhyming and category member generation but not phonological generation), neuroanatomical areas consisting of the left pre-supplementary motor area (preSMA), dorsal caudate, and ventral anterior (VA) nucleus of the thalamus were active. In addition, right basal ganglia activity in the caudate and putamen was present during the rhyming and semantic category generation tasks, in the relative absence of right frontal activity. Crosson and colleagues (2003) suggested that the left preSMA-caudate-VA thalamus serve as a frontal-striatal loop involved in word retrieval for language. Furthermore, they proposed that the right basal ganglia activity acts to suppress right frontal activity that may interfere with word production.

Additional support for the role of the basal ganglia in language paradigms comes from Crosson and colleagues (Crosson, Benjamin, & Levy, 2007) who have postulated that the basal ganglia may be involved in an early suppression, intermediate enhancement, and late suppression cycle of behavior during complex language tasks such as word generation. They suggested that the role of the basal ganglia for cognitive tasks may be similar to the enhancement and early and late suppression cycles suggested by Mink (1996) and Nambu and colleagues (2002) for motor behaviors that stem from the hyperdirect, direct, and indirect pathways of the basal ganglia, respectively. Within the language framework, Crosson and colleagues (2007) suggested that for a task such as word generation, there is an initial resetting of the system to allow for a previous item generated from a target category to become inactive. Enhancement for relevant new items for the category then occurs, providing

options for the next category exemplar for word generation. A second wave of suppression then occurs once a new exemplar is selected; this suppression allows for the new exemplar to be specifically selected and suppresses competing exemplars.

Empirical support for the early suppression-intermediate enhancement-late suppression cycle of basal ganglia neuroregulation in language functions can be derived from behavioral paradigms. Copland and colleagues (Copland, Chenery, & Murdoch, 2000; Copland, 2000; Copland, 2003) have demonstrated the implications of subcortical involvement in complex language tasks during controlled processing using behavioral semantic priming paradigms in patient populations with either ischemic basal ganglia lesions or Parkinson's disease (PD). Copland (2000) administered a word triplet priming task to PD patients, patients with nonthalamic subcortical lesions of the dominant hemisphere, patients with cortical lesions of the dominant hemisphere, and neurologically healthy controls. At a short stimulus onset asynchrony (SOA), all patient groups performed similarly to controls, demonstrating priming effects for concordant, neutral, and discordant triplets as compared to unrelated triplets, with the concordant word triplets exhibiting the strongest of the priming effects. At the long SOA, healthy adults continued to perform similarly to that of the short SOA with the exception that discordant triplet primes no longer exhibited a priming effect. In contrast at the long SOA, cortical lesion patients continued to prime for all four of the task conditions but lost differences between the priming conditions. More relevant within the context of the current study are the findings from the two patient populations with subcortical involvement, which suggest a loss of enhancement due to aberrant basal ganglia function. Nonthalamic subcortical lesion patients lost all priming effects, consistent with

a disruption of the direct loop and subsequent loss of enhancement at longer SOAs. PD patients showed priming only for the concordant condition at the long SOA, which suggests an inability to enhance responding for all but the strongest stimuli in Parkinson's disease.

Additionally, Copland (2003) has provided evidence of the basal ganglia's implications in the late-suppression part of the suppress-enhance-suppress cycle. A dominant-subordinate paired priming task using two SOAs was given to PD patients, patients with nonthalamic subcortical lesions of the dominant hemisphere, patients with cortical lesions of the dominant hemisphere, and healthy older controls. At the shorter SOA, all patient groups primed to both subordinate and dominant meanings. At the long SOA, healthy controls and patients with cortical lesions primed only to the dominant meaning for words, a finding similar to that found in healthy college-age subjects employing this paradigm across multiple SOAs (Simpson & Burgess, 1985). In contrast, both nonthalamic subcortical lesion and PD patients showed priming for both dominant and subordinate meanings at the long SOA, suggestive of a failure to suppress the subordinate meaning at the long SOA.

More recently, Castner and colleagues (2007) evaluated noun and verb generation in individuals with Parkinson's disease (PD) who had undergone bilateral STN deep brain stimulation (DBS) surgery as compared to healthy age-matched controls. They used a paradigm based on Peran and colleagues (2003) to evaluate noun and verb associate generation for aurally presented nouns and verb targets. Subjects were instructed to generate either a noun or a verb in response to either a noun or verb stimulus, and the experiment consisted of four types of production pairings: noun-noun,

verb-noun, noun-verb, and verb-verb. Most relevant to the current study were the findings for the noun-noun and verb-verb generation conditions. Castner and colleagues (2007) found that during the DBS off stimulation condition, PD participants exhibited more errors in verb generation but not noun generation as compared to healthy control participants. In addition, when STN DBS stimulation was on, PD participants displayed more errors during both noun and verb same pairing conditions (i.e., noun-noun, verb-verb conditions). These findings would suggest a possible enhancement failure that occurs in PD that may be specific to verb generation (as displayed by verb-verb generation deficits during the off stimulation condition) as well as a suppression failure amplified by STN DBS stimulation (as exhibited in noun and verb exemplar production during the STN DBS on stimulation state). The study by Castner and colleagues (2007) may provide some insight regarding verbal fluency findings during STN DBS stimulation in PD. While some verbal fluency studies in PD have not found fluency impairments during STN DBS (e.g., Dujardin, 2001), many studies of phonemic and/or semantic fluency in PD with STN DBS have reported impairments on phonemic and/or semantic fluency during STN DBS (e.g., Saint-Cyr, Trepanier, Kumar, Lozano, & Lange, 2000; Schroeder, Kuehler, Lange, Haslinger, Tronnier, Krause, Pfister, et al., 2003). Within the context of the findings reported by Castner and colleagues (2007), their findings would appear to suggest that a suppression failure may be induced during fluency tasks via stimulation of the STN.

CHAPTER 3
FUNCTIONAL NEUROIMAGING OF LANGUAGE IN NEUROLOGICALLY HEALTHY POPULATIONS

An appreciation of the aforementioned behavioral research in populations with subcortical pathology is essential for evaluating the implications of the current paradigm. However, in order to understand the current project's aims in studying healthy aging, it is also important to evaluate applicable neuroimaging findings in the domain of language. Specific neuroanatomical structures and networks, particularly in the left hemisphere, have been implicated in language processing and production. Neuroanatomical areas relevant to the current study include the left lateral frontal cortex (e.g., left inferior frontal gyrus) and left medial frontal cortices. For example, the left inferior frontal cortex, DLPFC (e.g., along the inferior frontal sulcus) and cingulate motor activity has been implicated in semantic tasks since the earliest neuroimaging studies in language (Peterson, Fox, Posner, Mintum, & Raichle, 1988). The role of the left inferior frontal cortex has been specifically implicated in the selection of semantic information among competing alternatives (e.g., Thompson-Schill, D'Esposito, Aguirre, & Farah, 1997) and switching functions during verbal fluency tasks (e.g., Hirschorn & Thompson-Schill, 2006).

Noun and verb retrieval functional neuroimaging results in neurologically healthy adults are particularly relevant for the current study. While there is limited neuroimaging research involving the study of verb retrieval, in one of the early neuroimaging studies of language, Warburton and colleagues (1996) used positron emission tomography (PET) to evaluate noun and verb retrieval in middle-aged adults (mean age of 48 years). Activation was found in left DLPFC, SMA, and anterior cingulate cortex for word retrieval in general, with more extensive activations patterns in these areas for verb

generation. Additionally, while subcortical findings were not discussed within the text of their article, Warburton and colleagues' results tables suggest subcortical differences in noun and verb retrieval in middle-aged adults and potential sensitivity of these paradigms for activating frontal-striatal circuits in word generation. For example, verb generation as compared to rest appeared to show significant activation bilaterally in the caudate head and thalamus, in the absence of right inferior frontal activity. These findings may be suggestive of similarities in verb generation as compared to the frontal-striatal implications provided from research in other types of word generation, e.g., category exemplar generation (Crosson et al., 2003).

Relatedly, Perani and colleagues (1999) investigated verb and noun processing using a lexical decision task and PET. They found that the language tasks evoked an extensive left hemisphere network of frontal and temporal cortex. Perani and colleagues (1999) also noted that while no region showed greater activation during decisions involving nouns as compared to verbs, the converse was not true; several regions were more active during the verb condition as compared to the noun condition, including left inferior frontal, left middle frontal, and right lenticular regions. Shapiro and colleagues (2005) recently compared noun and verb grammatical operations, reporting that verbs activated a left frontal cortical network whereas nouns activated a bilateral temporal network. Such results are supportive of recent transcranial magnetic stimulation (TMS) research demonstrating disruption of verb but not noun production when the left prefrontal cortex is suppressed using TMS (e.g., Cappelletti, Fregni, Shapiro, Pascual-Leone, & Caramazza, 2008).

With regards to functional imaging results in aging, Persson, Sylvester, Nelson, Welsh, Jonides, and Reuter-Lorenz (2004) recently compared verb generation in young and old adults using an fMRI task involving noun stimuli with either few or many competing alternatives for an appropriate verb response. Although the two age groups performed similarly behaviorally in terms of verb generation accuracy and response latency, they showed differences in regional brain activation. For both age groups, high selection demands activated several cortical regions, including bilateral frontal, left anterior frontal, left inferior temporal and dorsal anterior cingulate cortex. Frontal regions showing peak activations were located in Brodmann's area (BA) 45 and BA 46 in the inferior part of prefrontal cortex, with the left frontal region extending dorsally into BA 9. Between group comparisons revealed less activation for old as compared to young adults in the left inferior frontal gyrus, left inferior temporal gyrus, and anterior cingulate; however, greater activation was found in the right inferior frontal gyrus for old adults as compared to young adults. For left inferior frontal gyrus, there was a positive correlation between the fMRI signal and reaction time for young adults, with a negative pattern of correlation observed in old adults. In addition, during task contrasts, young adults showed stronger activity in dorsal frontal regions during the many competing alternatives task. Bilateral basal ganglia activation was found in old participants but not in young participants during contrasts between the many versus few competing alternatives conditions, which Persson and colleagues (2004) interpreted to be a compensatory response to the task.

Persson and colleagues' (2004) interpretation of greater activation in language non-dominant cortex and the basal ganglia as serving compensatory functions is not an

unfamiliar theme in the cognitive neuroscience of aging. Cabeza (2002) posited a model of cognitive performance in aging termed HAROLD (hemispheric asymmetry reduction in older adults). The HAROLD model suggests that old adults show less lateralized prefrontal activity during cognitive tasks as compared to young adults. While Cabeza (2002) originally discussed HAROLD as potentially resulting individually from compensation or dedifferentiation or acting in conjunction with one another, Cabeza and other cognitive neuroscientists studying aging differences in task performance more recently tend to interpret their findings within a compensatory framework (e.g., Cabeza, Daselaar, Dolcos, Prince, Budde, & Nyberg, 2004). However, several studies of language function by Crosson and colleagues have suggested that a compensatory role may be less clear of an interpretation for language studies of aging, such as object naming (Wierenga, Benjamin, Gopinath, Perlstein, Leonard, Rothi, et al., 2008) and category-member generation (Benjamin, McGregor, Chang, White, Rackelman, Sherod, et al., 2008; Cohen, Benjamin, McGregor, Chang, White, K. D., Rackelman, et al., 2009; Meinzer, Flaisch, Wilser, Eulitz, Rockstroh, Conway, et al., 2009). For example, during a picture naming study conducted by Wierenga and colleagues (2008), right inferior frontal, right precentral, and bilateral medial frontal activity was found in old as compared to young adults. When naming accuracy was correlated with the hemodynamic response (HDR) in regions of interest, “high” performing older adults demonstrated a positive correlation in the left and right inferior frontal gyrus (BA 45, 47) and a negative correlation in the right precentral gyrus and right superior frontal gyrus. “Low” performing older adults showed a positive correlation for the left inferior frontal (BA 44, 45, 47) and a negative correlation between accuracy and HDR in the right

inferior cortex. These differences within older adults suggested that the ability to recruit the right hemisphere may not be universally compensatory for all older adults and may be region specific, since the ability to recruit Broca's area homologue (right hemisphere) appeared to assist in naming performance in "high" performing older adults but not "low" performing older adults while the recruitment of other right frontal regions outside of inferior frontal gyrus were negatively correlated in "high" performing old adults.

CHAPTER 4
CLINICAL SUPPORT FOR DISTINCTIONS IN VERB-NOUN PRODUCTION

In addition to the results from behavioral paradigms in patient populations with frontal-striatal involvement already mentioned in Chapter 2, several research groups have demonstrated the importance of prefrontal cortex involvement for verb retrieval. Damasio and Tranel (1993) reported on the behavioral and neuroanatomical dissociation between noun and verb production in three clinical patients. Two of their patients performed similarly to controls on verb production but were impaired on noun production; these two patients had lesions in the left anterior and middle temporal lobe. In contrast, a patient with a lesion in the left premotor cortex showed the reverse pattern of behavior, demonstrating intact common and proper noun production and impaired verb retrieval. Similarly, Daniele, Giustolisi, Silveri, Colosimo, and Gainotti (1994) described two patients with left frontal lobe atrophy who were impaired on the naming and comprehension of verbs, whereas a third patient with left temporal lobe atrophy was impaired on noun naming. Thompson-Schill, Swick, Farah, D'Esposito, Kan, and Knight (1998) described impaired verb generation performance during high selection demands for individuals with lesions including the posterior region of the left inferior frontal gyrus, as compared to persons with left frontal lesions not involving this area and persons with right frontal lesions. While total lesion volume did not predict subjects' task performance, the percentage of damage to BA 44 was a significant predictor of selection-related and task errors.

Parkinson's disease (PD) has recently served as a clinical cohort of interest with regards to basal ganglia implications in verb retrieval. Cotelli and colleagues (2007) recently compared non-demented PD patients with age-matched controls on action and

object naming performance. PD subjects showed a deficit in both action and object naming as compared with controls. In addition, PD subjects but not controls performed significantly worse on action than object naming in that study. Using an action fluency task, Piatt and colleagues (1999a) found that action fluency but not semantic or phonemic fluency discriminated demented PD patients from non-demented PD patients and healthy controls and suggested that action fluency may be particularly sensitive to frontal-striatal pathophysiology. Piatt and colleagues (1999b) in a study of healthy older adults found significant moderate correlations between action fluency and measures of executive function such as the Wisconsin Card Sort Test (WCST) and Trails B. As mentioned previously, Castner and colleagues (2007) recently described behavioral evidence of subcortical involvement in noun and verb generation in PD. For patients with subthalamic (STN) deep brain stimulation (DBS), a higher number of errors during verb generation were made both on and off STN stimulation as compared to age-matched controls. In addition, PD subjects displayed a higher number of errors for noun production as compared to controls while STN stimulation was on.

CHAPTER 5
HYPOTHESES

The aforementioned studies suggested that implementing verb and noun generation paradigms may be useful for studying aging and clinical populations of interest with known frontal-striatal implications. The current study used functional magnetic resonance imaging (fMRI) and the noun-noun and verb-verb conditions for word generation as outlined by Castner and colleagues (2007) to investigate noun and verb generation and the involvement of cortical-subcortical pathways in aging. Specific study hypotheses were as follows:

Prediction 1: The direct basal ganglia pathway and "enhancement" difficulties will be implicated in aging, as measured using verb-verb word generation.

During their verb generation paradigm, Persson and colleagues (2004) found less activation for old as compared to young adults in the left inferior frontal gyrus, left inferior temporal gyrus, and anterior cingulate, while greater activation was found in the right inferior frontal gyrus for old adults as compared to young adults during their verb generation task. They interpreted the activation in right frontal cortex as serving a compensatory function for reduced activation in left cortical regions. Additionally, Castner and colleagues (2007) found that during their STN DBS off stimulation condition, PD participants exhibited a deficit in verb generation but not noun generation, suggesting an enhancement failure in PD that may be specific to verb generation. Therefore, hypotheses for the current verb-verb word generation were the following:

Hypothesis 1a: Significantly less left cortical and subcortical activity was expected for the old as compared to the young subject group.

Hypothesis 1b: Significantly more right cortical and subcortical activity was expected for the old as compared to the young subject group.

Prediction 2: The indirect basal ganglia pathway and "suppression" difficulties will also be implicated in aging, as measured using noun-noun word generation.

Crosson and colleagues (2003) have demonstrated that during category generation for nouns, neuroanatomical areas consisting of the left pre-supplementary motor area (preSMA), dorsal caudate, and ventral anterior (VA) nucleus of the thalamus are active. In addition, right basal ganglia activity in the caudate and putamen is also present during category generation, in the relative absence of right frontal activity. They suggested that the left preSMA-caudate-VA thalamus serves as a frontal-striatal loop involved in word retrieval for language and that right basal ganglia activity may act to suppress right frontal activity that may interfere with language production. In the study conducted by Wierenga and colleagues (2008), right inferior frontal, right precentral, and bilateral medial frontal activity was found in old as compared to young adults during picture naming. Castner and colleagues (2007) found that during STN DBS stimulation, PD participants displayed more errors during both noun and verb same pairing conditions (i.e., noun-noun, verb-verb conditions). These findings would suggest a suppression failure amplified by STN DBS stimulation exhibited in noun and verb exemplar production during the STN DBS on stimulation state. Based on these findings, hypotheses for noun-noun word generation were the following:

Hypothesis 2a: Significantly greater left cortical and subcortical activity was expected in the old, as compared to young, subject group.

Hypothesis 2b: Significantly greater right cortical and subcortical activity was expected for the old, as compared to the young, subject group.

CHAPTER 6
METHODS

Participants

Fifteen young adults between 18 and 35 years of age (7 female) were recruited from the Gainesville community and 15 older healthy adults at least 70 years of age (8 female) were recruited from the Gainesville community and from a recruitment mailer sent to the research registry of the University of Florida's Claude D. Pepper Older Americans Independence Center. All of the older participants were Caucasian, as were 80% of the younger participants. Education level was similar between the two groups, with both groups consisting on average of college-educated subjects. Older and younger participants did not differ significantly according to level of education, $t(28) = .54$, $p = .60$ (see Table 1). All participants spoke English as their first language and were right-handed as determined by the Edinburgh Handedness Inventory (EHI; Oldfield, 1971). Medical exclusionary criteria included history of dementia or Mild Cognitive Impairment, head trauma, neurological disorder (e.g., stroke), learning disability (e.g., dyslexia), psychiatric disorder (e.g., schizophrenia), drug or alcohol abuse, and chronic medical conditions and medical procedures likely to impair cognition (e.g., renal or hepatic failure, coronary artery bypass grafting). Pharmacological exclusionary criteria included benzodiazapines, antiepileptic, antipsychotic, dopaminergic, and anticholinergic classes of medications, due to their potential effects on cognition. Given that the main outcome measures of the current proposal involve fMRI, individuals with pacemakers, metal implants, claustrophobia, or other conditions contraindicated for MRI were excluded from the current study. Young female participants were excluded if they were pregnant or trying to become pregnant. Three

additional young subjects were initially enrolled but excluded from the current analyses due to failing to complete all testing or fMRI appointment tasks. Seven additional old subjects were initially enrolled but excluded from the study analyses. Two of the excluded old subjects completed testing but did not meet criteria for continuing to participate in the fMRI portion of the study due to testing performance that did not meet healthy control enrollment criteria as outlined below. An additional four old subjects were excluded due to subjective memory complaints or the disclosure of neurological problems following their testing session. Lastly, one old subject who participated in fMRI was excluded from the current analyses due to an incidental structural MRI finding suggestive of an asymptomatic cortical abnormality.

Participants were instructed to abstain from caffeine for at least 2 hours prior to the fMRI scanning session. Informed consent was obtained from participants according to guidelines established by the Health Science Center Institutional Review Board at the University of Florida. Participants were paid $25 for participation.

Procedures

Neuropsychological testing

Prior enrollment in the fMRI study, participants were administered a standard health history questionnaire and completed a short neuropsychological assessment to screen for possible dementia and Mild Cognitive Impairment-anmestic type (aMCI). Amnestic Mild Cognitive Impairment (aMCI) is a precursor to pathological aging and is a high-risk condition for the development of clinically probable Alzheimer's disease (Peterson et al., 2001). Criteria for aMCI include self- and/or corroborated memory complaint, impaired memory function for age and education level, preserved general cognitive functioning, intact activities of daily living, and impairments not currently

meeting criteria for dementia. Notably, none of the participants included in the current study reported subjective language or memory complaints in daily life.

Neuropsychological assessment included several tests to assess language, memory, and executive skills, in order to rule out dementia and aMCI and for determining potential group differences in neuropsychological test performance that may either contribute to or be independent of the fMRI findings. The Mini Mental State Exam (MMSE; Folstein, Folstein, & McHugh, 1975) was administered, and all subjects participating in fMRI scored 27 or above on the MMSE, which is a standard research cutoff since MMSE scores below 24 are likely indicative of cognitive impairment. The California Verbal Learning Test, Second Edition (CVLT-II; Delis, Kramer, & Kaplan, 2000) was used to assess verbal learning and memory. Since patients with mild dementias may perform normally on the MMSE but display memory difficulties, participants scoring greater than 1.5 SD below the mean for age-appropriate norms on Long-Delay Free Recall and Recognition Memory were assumed to have a verbal memory deficit and thus were excluded from the fMRI portion of the study. The Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 2001), a 60-item confrontation object naming test, was administered to assess participants' abilities to name objects. The Action Naming Test (ANT; Obler & Albert, unpublished), a 55-item confrontation action naming test, was administered to assess participants' abilities to name actions. Several brief word generation tasks were administered to assess executive language and cognitive functions in the two participant cohorts. The Verbal Fluency subtest of the Delis-Kaplan Executive Function System (D-KEFS; Delis, Kaplan, & Kramer, 2001) was given in order to assess phonological fluency, semantic fluency, and semantic fluency

switching abilities. During the phonological fluency portion of Verbal Fluency, participants were given 3 letters (i.e., F, A, S) and asked to generate items beginning with each letter. The semantic fluency portion of Verbal Fluency required participants to generate items belonging to a semantic class (i.e., animals, boys' names). The Verbal Fluency category switching subtest assessed participants' abilities to switch between providing items for 2 categories (e.g., fruits, furniture). The Action Fluency Test (Piatt, Fields, Paolo, et al. 1999) was administered to assess action fluency and generation abilities and consists of providing exemplars of actions that people perform. The Homophone Meaning Generation Test (HMGT; Warrington, 2000) consisting of 8 homophones for which a number of alternate word definitions can be generated (e.g., "tick") was administered to measure of the ability to switch between verbal concepts.

Noun-Verb Experimental FMRI Paradigm

Stimuli for the fMRI study were presented visually and projected onto a screen position above the participant's head using the Integrated Functional Imaging System (IFIS) and E-Prime version 1 software. The fMRI paradigm consisted of the noun-noun and verb-verb generation tasks outlined by Peran and colleagues (2003) and Castner colleagues (2007). Three fMRI runs consisting of a block design were used. Each run consisted of 8 blocks of noun generation and 8 blocks of verb generation, for a total of 404 seconds per fMRI run. Each of the 16 blocks presented consisted of either 3 nouns or 3 verbs presented in randomized trial blocks, with 24 total noun and 24 total verb generations per run. Thus, a total of 72 nouns and 72 verbs were visually presented during the functional imaging session. Resting blocks consisting of a visual fixation cross were presented at the beginning and end of each fMRI run and between each 3-item trial block. Resting blocks were pseudo-randomized and contained 10, 12, or 14

seconds of rest in order to allow the hemodynamic response to return to baseline prior to the next stimuli block presentation. Rest blocks of randomized length were used to mitigate the effects of periodic or quasi-periodic physiological noise, and a simple visual fixation rather than a passive language-based control task was used to maximize the possible amount of activity for the experimental condition (Newman, Twieg, & Carpenter, 2001). Each noun or verb within a block was presented for 2 seconds, and an additional 2 seconds were allowed for an associated within-grammatical class response to be covertly generated by the participant. The timing for the fMRI noun-noun and verb-verb generation tasks was modified for fMRI presentation but consistent with that used in healthy older adults during the previous behavioral paradigms (Peran, Rascol, Demonet, et al. 2003; Caster, Chenery, Silburn, et al. 2007). Noun and verb probe stimuli were derived from Lu and colleagues (2002) and from stimuli available through the International Picture Naming Project (IPNP, 2009) and equated between the generation conditions for word frequency in the English language (Francis and Kucera, 1982). One additional run of 8 noun and 8 verb blocks was administered outside of the scanner prior to the functional imaging session. The 4 noun-verb runs were counterbalanced so that across participants in each age group, each of the 4 runs were used 25% of the time as a practice run and 75% of the time during the fMRI experiment. The additional run outside of the fMRI session allowed both for practice outside of the scanner prior to fMRI data collection and provided an estimate of subject performance on the covert generation task in the scanner.

Image Acquisition

Images were acquired on a Philips 3 Tesla Achieva instrument with an 8-channel SENSE multiple arrayed head coil. Head motion was minimized using foam padding.

Functional images were obtained with a 1-short gradient echo planar functional imaging (EPI) scan (TR=2000ms; TE=30ms; FOV=240mm; matrix size=64 x 64; 3mm x 3mm in-plane resolution, FA=80^{o}). Thirty-eight 3mm thick axial slices covering the whole brain were acquired in the axial plane. A high-resolution T1-weighted anatomic scan (TR=8.1ms; TE=3.7ms; FOV=240mm; FA=8^{o}; matrix size=240 x 240; 180 1.0mm slices; sagittal orientation) was obtained prior to functional imaging to provide anatomic reference. A T2-weighted anatomic scan was collected in order to verify that subjects did not have incidental neuroanatomical findings that would preclude them from meeting criteria as a healthy control (TR=2500ms; TE=250ms; FOV=175mm; FA=90^{o}; matrix size=224x223; 64 4.5mm slices; axial orientation). Head motion was minimized using foam padding.

Data analysis

Behavioral data

Performance accuracy on the noun-verb task for the one run completed outside of the scanner was compared between the 15 old and 15 young participants using independent samples t-tests. Performance on the memory and language measures was also compared between the two age groups using independent samples t-tests.

Neuroimaging data and FMRI analyses

FMRI data were analyzed and overlaid onto structural images using the Analysis of Functional Neuroimaging (AFNI) software from the National Institutes of Health (Cox, 1996). The first 6 images of the 3 functional runs were discarded to ensure attainment of steady state. Time series images were spatially registered in three-dimensional space using AFNI's 3dvolreg program, in order to minimize the effects of head motion. Images were visually inspected for gross artifacts and quality control procedures were

applied to the data to detect residual motion or susceptibility artifact. For each of the subjects, the 3 imaging runs for the FMRI task were detrended of low frequency signal drifts (Birn, Saad, and Bandettini, 2001) and concatenated into a single time series. Prior to deconvolution and functional analyses, functional images were spatially smoothed with a Gaussian kernel of 4mm full-width at half-maximum (FWHM) to compensate for variability in structural and functional anatomy across participants. For each voxel, the observed fMRI intensity timeseries was modeled as the convolution of the experimental stimulus vector (comprised of 24 blocks of covert noun and 24 covert verb generation) and the estimated best-fit twelve-lag impulse response function (IRF), allowing the hemodynamic response (HDR) to return to baseline. Signal timeseries were Z-normalized within runs to mitigate signal intensity variance between runs and participants.

The dependent variable for analyses was the area under the curve (AUC) of the estimated IRF generated from AFNI's 3dDeconvolve program. AUC was calculated by adding the deconvolved image intensity at each deconvolved time point of the impulse response. The T1-weighted anatomic images and the deconvolved functional activation maps were warped to the co-ordinates of the co-planar stereotaxic atlas of Talairach and Tournoux (1988) as implemented by AFNI and resampled at a $1mm^3$ resolution. Within group comparisons of word generation to a baseline of passive viewing was conducted using voxel-wise t-test (AFNI's 3dttest) for young and old adults for noun and verb generation separately using the IRF AUC, and independent samples t-tests were conducted to compare young versus old adults on the two generation tasks. A cluster thresholding technique using a Monte Carlo simulation (AFNI's AlphaSim progam) was

implemented for whole brain analyses to determine which areas of activation on the t-maps were significant at single voxel p-value levels of <.001 for independent measures t-tests. Based on the Monte Carlo simulation, the independent samples t-tests required contiguous voxel cluster sizes of 78 microliters or greater for cortical and subcortical regions of interest across the whole brain to maintain a cluster significance level of p<.05 and thus protect from Type I error. In addition to whole brain fMRI cluster analyses, bilateral subcortical and cortical areas involved in language generation were specifically evaluated as regions-of-interest (ROIs) using anatomical masks available in AFNI. ROIs were selected on the basis of previous empirical work from our laboratory (Crosson, Benefield, Sadek, et al. 2003; Crosson, Sadek, Bobholz, et al. 1999) and upon conceptual consideration of semantically based word generation (Crosson, Benjamin, & Levy, 2007). These anatomy-based ROIs included the STN, caudate nucleus, globus pallidus, thalamus, lateral inferior frontal cortex (IFG) corresponding with Broca's region (BA 45, BA 44, and BA 6), middle frontal gyrus (MFG; in order to include cortex around the inferior frontal sulcus), and medial frontal cortex consisting of pre-SMA, SMA, and rostral cingulate zone (BA 6 and BA 32).

CHAPTER 7
RESULTS

Neuropsychological testing

Performance data on the neuropsychological test battery is summarized in Table 8-1. Performances between young and old participants were similar on several measures, including the ANART predicted IQ score, CVLT-II age-corrected total for 5 learning trials and long-delay free recall, BNT raw score, ANT raw score, DKEFS age-corrected phonemic fluency, category fluency, and category switching, and the HMGT verbal concept generation. Performance differed between the two groups for the age- and education-corrected BNT scores, $t(28) = -4.16$, $p < .01$, with young adults obtaining lower age- and education-corrected object naming scores than old adults despite similar BNT raw score performance. Performance differed between the two groups for Action Fluency, $t(28) = 2.80$, $p < .01$, and the DKEFS category fluency raw score, $t(28) = 3.71$, $p < .01$, with old adults generating fewer responses than young adults on both tasks.

Noun and verb generation outside of the fMRI scanner

Performance accuracy for both noun-noun and verb-verb generation was lower for the old adults as compared to the young adults in the noun and verb generation run collected prior to fMRI scanning, $t_{Noun}(28) = 3.09$, $p = .004$; $t_{Verb}(28) = 5.04$, $p < .001$, (see Table 8-1).

FMRI results: Old versus young noun and verb generation comparisons

Whole brain fMRI results comparing old to young for each generation task are summarized in Table 8-2 and displayed in Figure 8-2. During noun generation, the largest significant clusters of activity were found for old adults as compared to young adults in the right precentral gyrus and left angular gyrus. Repeated measures

ANOVAs performed on the average IRF for each of these two regions suggests significant Group x Time interactions for the IRF time course during noun generation, Wilks' Lambda = .21, $F_{Rprecentral}$ (12, 348) = 5.51, p = .001; Wilks' Lambda = .30, $F_{Langular}$ (12, 348) = 3.35, p = .012. Figure 2 indicates that for the right precentral gyrus cluster, old participants showed an increase in activity relative to baseline, whereas young participants showed a decrease in activity relative to the visual fixation baseline. In contrast, both age groups showed some increase in activity in the left angular gyrus, with greater activity for the old adults. Other smaller clusters of significant activity for noun generation were found in the low part of the precentral gyrus, the supramarginal gyrus, the superior parietal lobe, and the middle temporal gyrus.

During verb generation, the largest significant perisylvian clusters of activity were found in the junction between right inferior frontal and middle frontal cortex and in left angular gyrus. Repeated measures ANOVA data for these two regions indicates differences in the IRF time course during verb generation for the left angular gyrus but not for the right inferior frontal/middle frontal gyral junction, although individual time points along the IRF time course were significant for both, Wilks' Lambda = .24, $F_{Langular}$ (12, 348) = 4.40, p = .003; Wilks' Lambda = .45, $F_{RIFG/MFG}$ (12, 348) = 1.73, p = .146. Figure 8-2 indicates that the differences between time points for the right inferior frontal gyrus reflect a main effect for age, Wilks' Lambda = .22, $F_{RIFG/MFG}$ (12, 28) = 4.30, p = .004, rather than an age X time interaction. For the left angular gyrus, old participants showed strong positive activity relative to baseline, similar to their response for noun generation, but the young adults showed little evidence of a response, in contrast to a

small response in the noun condition. No areas were significantly greater for young participants as compared to old participants in either the noun or verb generation.

Table 8-3 presents performance data for noun and verb generation outside of the scanner for each participant group correlated with AUC data for each of the 4 clusters from Figure 8-2. Pearson product-moment correlations were done for each participant group's noun and verb generation accuracy outside of the scanner and for each of the 4 significant clusters. None of these areas was significantly correlated with task performance for either condition for either group.

Young versus baseline noun and verb generation comparisons

Results for the noun and verb generation tasks as compared to the baseline rest condition for the young participants are outlined in Table 8-4. In sum, cortical activity was fairly similar between noun and verb generation for medial frontal cortex bilaterally (BA 6, 8, and 32) and in both left and right lateral frontal regions (inferior and middle frontal gyri), except that activity does not extend into the middle frontal gyrus on the right. Both tasks elicit activity in the left superior and middle temporal gyri, but there is a small volume of activity in the left supramarginal gyrus for verb but not noun generation. Subcortical activity was also similar between noun and verb generation in the left caudate and right putamen.

Old versus baseline noun and verb generation comparisons

Results for the noun and verb generation tasks as compared to the baseline rest condition for the old participants are outlined in Table 8-5. In keeping with the comparison of old vs. young across task, these within task comparisons for old subjects showed both a greater number of clusters and a greater volume of activity within many clusters than young subjects showed. In addition, cortical activity was fairly similar

between noun and verb generation and extensive for medial frontal cortex bilaterally (BA 6, 8, and 32) and in both left and right lateral frontal regions (primarily precentral, inferior, and middle frontal gyri). Subcortical activity was found in the left caudate and left pulvinar for both generation conditions and in the right putamen during noun generation. There was ample posterior perisylvian activity (STG, angular gyrus, SMG) in both hemispheres for both tasks.

A priori ROI AUC time course data

Tables 8-6 and 8-7 and Figures 8-3 and 8-4 summarize significant area under the curve (AUC) repeated-measures ANOVA data for young versus old time course comparisons in proposed frontal cortical and subcortical regions of interest (ROIs) using AFNI anatomical masks for IFG, MFG, medial frontal, STN, caudate, globus pallidus, and thalamus. For cortical ROIs, significant Group x Time interactions were found during noun generation between young and old at p<.05 for right inferior frontal gyrus, Wilks' Lambda = .35, F_{RIFG} (12, 348) = 2.59, p = .036, right middle frontal gyrus, Wilks' Lambda = .30, F_{RMFG} (12, 348) = 3.29, p = .013, and right medial cortex, Wilks' Lambda = .32, $F_{RMedial}$ (12, 348) = 2.95, p = .02. A significant Group x Time interaction was found during verb generation between young and old at p<.05 for right inferior frontal gyrus, Wilks' Lambda = .36, F_{RIFG} (12, 348) = 2.51, p = .04. None of these areas significantly differed between the groups using a more conservative p<.0125 cut-off to correct for multiple statistical comparisons.

For subcortical ROIs, significant Group x Time interactions were found at p<.0125 for the left and right STN during noun generation, Wilks' Lambda = .27, F_{LSTN} (12, 348) = 3.78, p = .006; Wilks' Lambda = .24, F_{RSTN} (12, 348) = 4.56, p = .002, with old subjects showing greater positive IRFs than young subjects. A Group x Time

interaction was also found in the left caudate during noun generation at p<.0125, Wilks' Lambda = .23, $F_{LCaudate}$ (12, 348) = 4.82, p = .002, with young subjects demonstrating greater positive IRFs than old subjects. While no other subcortical ROIs were significant at the more conservative p<.0125 statistical threshold, Group x Time interactions were found at p<.05 in the right caudate during noun generation, Wilks' Lambda = .36, $F_{RCaudate}$ (12, 348) = 2.54, p = .04, and in the right STN and right thalamus during verb generation, Wilks' Lambda = .38, F_{RSTN} (12, 348) = 2.34, p = .05; Wilks' Lambda = .32, $F_{LCaudate}$ (12, 348) = 3.01, p = .02. Right STN verb generation IRFs were similar to those seen in the STN during noun generation, with greater positive IRFs in old versus young adults. The IRFs for the right caudate during noun generation is similar to that seen in the left caudate, with greater positive IRF in young versus old subjects. The IRFs in right thalamus during verb generation suggest differences in time courses for the 2 subject groups, with higher positive IRFs in old versus young subjects in the first half of the time course that returns to baseline by image 10, with the young subjects showing a positive biphasic IRF during the 13-image time course.

Noun versus verb generation in young and old adults

No significant differences were found between the noun and verb generation tasks when all subjects were combined together for statistical analysis, nor were there significant task differences when separate within-group analyses were conducted for the old or young participant groups separately to evaluate differences in noun versus verb generation.

CHAPTER 8
DISCUSSION

Results from the current study suggest aging differences for old as compared to young subjects with regards to noun and verb generation. First, for cortical regions and the fMRI between-group comparisons, the current study found greater activation in old as compared to young subjects in the right precentral gyrus during noun generation, the right inferior frontal sulcus during verb generation, and the left angular gyrus during both generation tasks. Findings in the right precentral gyrus during noun generation and the right inferior frontal sulcus during verb generation are consistent with the proposed hypotheses that the old subjects would show greater activity in right frontal cortical regions for both noun and verb generation. However, while it had originally been proposed that less left frontal cortical activity would be present in old adults during verb generation and greater left frontal activation during noun generation in old adults based on other studies, there were no between-group differences in left frontal cortical activation. While the left angular gyrus and other left posterior language cortices were not a primary focus of the current study, the findings in the left angular gyrus are not surprising, given its role in semantic processing and imaging results demonstrating positive activation during semantic processing tasks in healthy adults (see Binder, Desai, Graves, and Conant, 2009 for a review).

In general, the current study's right frontal findings are consistent with aging research that suggests greater right hemisphere activity (hemispheric asymmetry reductions) in older adults as compared to young for completing cognitive tasks (e.g., Cabeza, 2002). However, specific results from this study suggest that a compensatory interpretation may not be as parsimonious as proposed by some healthy aging

researchers. As mentioned in the results, the right precentral gyrus findings during noun generation stemmed from the combination of greater positive activity in old adults and negative IRF in the young adults for that region. Negative IRF has been reported recently in young adults in the non-dominant hemisphere for motor tasks (e.g., McGregor, et al., 2011), suggesting that at least for young adults, suppression of a task's non-dominant hemisphere occurs in order for optimal performance on motor tasks whereas the old adults may recruit the non-dominant region to complete such tasks. This concept of non-dominant hemisphere suppression has implications for language research in healthy aging, since while similar to the HAROLD aging model of reduced hemispheric asymmetry with aging, the study by McGregor and colleagues suggests that that the asymmetry may not necessarily facilitate task performance in older adults but rather, in some tasks, the non-dominant hemisphere's lack of suppression may in part interfere with task performance. Additionally, right hemisphere activation during language studies may not be universally compensatory within older adults or even within frontal cortical regions as a whole. During the picture naming study conducted by Wierenga and colleagues (2008), right inferior frontal, right precentral, and bilateral medial frontal activation was generally found in old as compared to young adults. However, old adults who performed better on the naming task specifically demonstrated a positive correlation between naming accuracy and the inferior frontal gyrus bilaterally, while negative correlations were found for that subset of subjects between task accuracy and activation in the right precentral gyrus and right superior frontal gyrus. Furthermore, old adults with lower performance in the naming study showed a positive correlation between naming accuracy and left inferior frontal

cortex and a negative correlation between naming performance and right inferior frontal activation. These differences within older adults for naming suggests that the ability to recruit the right hemisphere may not be universally compensatory, since the ability to specifically recruit Broca's area homologue (right hemisphere) appeared to assist in naming performance in old adults, whereas recruitment of other right frontal regions were negatively correlated with performance. With regards to the current study, the greater left (but not right) posterior perisylvian activity in old adults suggests that compensatory models such as HAROLD implicating greater use of the task non-dominant hemisphere for older adults may apply only for more anterior cortical regions. Within the context of the current study, greater right hemisphere activity for old than young adults involved more anterior regions such as inferior frontal and precentral cortex, whereas posteriorly greater activity for old than young adults was found primarily in the left hemisphere.

The subcortical results for the noun and verb generation tasks are also more complex than as had originally been proposed. FMRI ROI analyses did not demonstrate significant between-group differences in subcortical regions at the conservative thresholding criteria used in the current study. However, a priori anatomy-based ROI analyses showed greater activity for old adults bilaterally in STN for noun generation, consistent with the idea that greater cortical and subcortical activity would be demonstrated bilaterally in old adults to complete the noun generation task, based on literature implicating the "indirect" pathway in noun generation. In addition, using a less stringent statistical threshold, the right STN activation in verb generation was greater for old subjects as compared to young subjects. Overall, the noun generation

STN findings are consistent with study hypotheses that old adults may show greater activity bilaterally, suggesting greater bilateral activity may be necessary in older adults in order to “suppress” competing responses during noun generation via the indirect pathway. Moreover, the greater right subcortical activity in old adults during verb generation appears to be congruent with the premise that if there were less language dominant (left) hemisphere activity, this may require greater right hemisphere activity in order to compensate for an attenuated left hemisphere “enhancement” effect via the “direct” pathway during verb generation in old adults. Generally speaking, the current STN findings are in line with recent thought that the STN may participate in cognitive tasks (Crosson et al., 2007) similar to how it participates in motor tasks through the “hyperdirect” (e.g., Nambu et al., 2002), “direct” and “indirect” pathways (Mink, 1996).

Differences in the caudate nucleus bilaterally during noun generation for the current study suggest that there is greater caudate activity in young than old adults. It may be that the greater left caudate activity in young adults within the context of noun generation could be interpreted as serving the function to provide adequate “enhancement” via the “direct” pathway” specific to the left hemisphere during noun generation for that age group. This line of interpretation appears to be supported by the greater right prefrontal activation found during noun generation for old adults, with the findings in old adults suggestive of non-dominant hemispheric recruitment in order to complete the noun generation task. As for the greater right caudate activity in young adults, this finding may implicate the “indirect” pathway and “suppression” within the non-dominant hemisphere for young adults, with such an interpretation supported by the

negative IRF findings in the right precentral gyrus for young subjects during noun generation, in contrast with the positive IRF data for old subjects in that area.

Overall, as the individual group comparisons to baseline for both noun and verb generation suggests, both generation tasks evoked increased activity in left lateral frontal regions such as inferior frontal gyrus, medial frontal, and left subcortical regions that have been found to be active during category member (noun) generation studies in healthy young subjects (e.g., Crosson, et al., 2003, Crosson, et al., 2001) as well as healthy aging studies evaluating noun word generation (e.g., Cohen, et al., unpublished) and object picture naming (Wierenga, et al., 2008) in healthy old adults. Additionally, for both age groups in the current study, right lateral frontal activity was present in both types of word generation, suggesting that the young subjects as well as the old were using bilateral lateral frontal networks in order to complete the tasks in the current study. As such, these findings suggest that the current covert word generation paradigms activate a similar network for word generation, regardless of the type of generation, but that the activity may be bilateral for both conditions and both age groups in order to complete this type of word generation task. The exception to this rule of thumb is in those right frontal clusters (precentral/postcentral gyri for noun, inferior frontal gyrus for verb) that showed greater activity for old than young adults. In these areas, young adults tend to show decreased activity, while old adults show increased activity. With regards to the left hemisphere activity, the limited spatial segregation found in the current study for the two types of word production is in line with a recent review of neuroimaging tasks to date evaluating nouns and verbs across various types of language paradigms (see Crepaldi, Berlingeri, Paulesu, & Luzzatti, 2011). One

previous study of noun and verb semantic fluency in healthy adults (Warburton, et al., 1996) found that verb generation produced greater activation than noun generation in the left inferior frontal gyrus, left SMA, left temporal sulcus, left temporo-parietal junction and left inferior parietal lobe whereas noun generation compared to verbs activated right superior frontal sulcus and left anterior cingulate gyrus. However, in the current study, no cortical or subcortical area in either hemisphere was more active during either generation condition. As such, the current study's results suggest that the word generation frontal activation may be bilateral for both conditions and both age groups, with the sole exception for each task mentioned above, in order to complete word generation using the current paradigms.

The current study sought to establish whether a behavioral noun and verb generation task used in patient populations with frontal-striatal dysfunction could be implemented with adequate sensitivity for evaluating age-related differences in noun and verb generation using fMRI. While the current study appeared to be adequate in terms of the subject sample and general experimental design to detect some differences in old versus young adults, there were several limitations of the current study. First, there are methodological aspects to fMRI in general that pose limitations to studying language paradigms such as the current one within the context of frontal-striatal circuitry. The temporal resolution of fMRI does not lend itself well for delineating which pathways may be primarily responsible for the results found during noun and verb generation or how such pathways may work in conjunction with one another during such a paradigm. Given that fMRI tasks and the related IRF operate on a scale of seconds whereas the timing as proposed by motor studies of the STN indicates that the cycle of

the hyperdirect-direct-indirect cortical-subcortical circuitry operate on a scale of milliseconds, studies such as the current one have to draw conclusions for results without clear temporal data to delineate the unique contributions of each pathway. Secondly, the fMRI experimental paradigm used in the current study was a covert word generation task. Covert word generation was chosen so that a block fMRI experimental paradigm presentation could be used, in order to increase statistical power and provide greater sensitivity for detecting group differences in subcortical structures (Crosson, et al., 2003). However, covert word generation paradigms are limited in that they do not provide direct information on performance accuracy, since the subject is not speaking aloud during the scanning session. Although one experimental run of the generation task was done outside of the scanner prior to the fMRI session, in order to ensure that participants understood the task and could adequately perform the task, accuracy for the experimental run outside of the scanner can only be interpreted an estimate of fMRI task performance. Third, while the time allotted for covert generation was similar to that used in the behavioral paradigm counterpart, given that the old subjects' accuracy on the word generation run outside of the scanner differed from that of the young subjects suggests that slightly more time may have been needed for similar performance accuracy in generation to occur.

The current study suggests that while typical word generation models often use noun generation (e.g., category generation, phonemic fluency), verb generation is a viable alternative for neuroimaging studies of word generation. While the current study was of a preliminary nature and used whole brain scanning, the between-group differences in STN and caudate activity relative to baseline findings for both subject

groups suggests that subcortical structures are active in this type of word generation. Given the paradigm's sensitivity for detecting subcortical activation, more region-specific functional neuroimaging that encompasses primarily subcortical and frontal cortices may be viable in future endeavors contrasting noun and verb generation, in order to achieve better spatial delineation of frontal-subcortical activation in these tasks. Secondly, the current study did not evaluate differences within grammatical class for the types of nouns or verbs generated (e.g., living versus nonliving nouns; human versus nonhuman verbs). While the current study did not propose to examine whether there are substrate variations for different types of nouns and verbs generated, future directions for these types of paradigms may include evaluating whether the grammatical class of items (i.e., nouns versus verbs), the semantic attributes of classes of items across grammatical classes (i.e., physical attributes versus items suggesting manipulability such as tools/human actions), or level of selection constraint (i.e., high selection constraint/few alternatives verus low constraint/many alternatives) may produce different patterns of activation (Crosson, et al., 2003). Lastly, the current study did not further parse subjects within groups by level of performance due to the number of subjects and the fact that accuracy data was not collected during the 3 fMRI runs. However, results from at least one noun picture naming study have suggested that there can be differences within older adults with regards to correlations between behavioral performance and fMRI activation patterns (e.g., Wierenga et al, 2008), suggesting that this can be an important consideration, should this type of paradigm be done as an overt word generation paradigm in future studies.

Table 8-1. Demographic and neuropsychological testing data for young and old subjects.

Variable	Young Mean (SD)	Old Mean (SD)	t-test or χ^2	p-value
Demographics				
Age (years)	23.20 (3.76)	76.67 (5.07)	t (1,28) = -32.81	p < 0.001***
Education (years)	16.00 (2.07)	15.50 (2.97)	t (1,28) = 0.54	p = 0.60
Women/men	7/8	8/7	χ^2 = 0.13	p = 0.72
Global Cognition				
MMSE	29.48 (1.25)	28.80 (0.86)	t (1,28) = 1.74	p = 0.10
ANART	117.19 (4.19)	117.74 (5.53)	t (1,28) = -0.30	p = 0.77
Learning and Memory				
CVLT List 1-5 Total Recall raw score	58.67 (10.73)	45.87 (8.39)	t (1,28) = 3.09	p = 0.005**
CVLT List 1-5 Total Recall T score	57.60 (12.67)	58.13 (9.58)	t (1,28) = -0.09	p = 0.93
CVLT Long Delay Free Recall raw score	13.27 (3.20)	9.93 (3.28)	t (1,28) = 2.82	p = 0.009**
CVLT Long Delay Free Recall z score	0.47 (1.27)	0.50 (0.89)	t (1,28) = -0.08	p = 0.93
Language				
BNT raw score	55.67 (2.09)	56.67 (2.41)	t (1,28) = -1.21	p = 0.24
BNT T score	46.20 (6.95)	59.07 (9.77)	t (1,28) = -4.16	p < 0.01**
ANT raw score	53.87 (2.00)	54.47 (1.92)	t (1,28) = -0.84	p = 0.41
DKEFS Letter Fluency raw score	47.07 (11.90)	41.53 (13.84)	t (1,28) = 1.18	p = 0.25
DKEFS Letter Fluency scaled score	13.00 (3.32)	12.07 (3.63)	t (1,28) = 0.74	p = 0.47
DKEFS Category Fluency raw score	46.67 (7.90)	35.07 (9.06)	t (1,28) = 3.74	p = 0.001***
DKEFS Category Fluency scaled score	13.47 (3.20)	11.47 (2.80)	t (1,28) = 1.82	p = 0.08
DKEFS Category Switch raw score	15.07 (2.76)	13.13 (2.83)	t (1,28) = 1.90	p = 0.07
DKEFS Category Switch scaled score	11.93 (3.20)	11.73 (2.99)	t (1,28) = 0.18	p = 0.86
DKEFS Switch Accuracy raw score	13.60 (3.09)	11.93 (3.34)	t (1,28) = 1.42	p = 0.17
DKEFS Switch Accuracy scaled score	11.67 (3.11)	11.33 (3.02)	t (1,28) = 0.30	p = 0.77
Action Fluency raw score	22.67 (5.86)	17.40 (4.32)	t (1,28) =2.80	p = 0.009**
HMGT raw score	27.47 (4.42)	27.60 (5.64)	t (1,28) = -0.07	p = 0.94
FMRI task: noun generation raw score	21.93 (1.83)	18.86 (3.28)	t (1,28) = 3.09	p = 0.004**
FMRI task: verb generation raw score	20.73 (2.22)	15.93 (2.89)	t (1,28) = 5.04	p <.001***

BNT = Boston Naming Test; ANT = Action Naming Test; DKEFS = Delis-Kaplan Executive Function Systems; HMGT = Homophone Meaning Generation Test. * = p<.05. ** = p<.01. *** = p<.001.

Table 8-2. FMRI region of interest (ROI) area under the curve time course data. Young versus old t-test comparisons for noun and verb generation.

Noun ROIs Old > Young	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)	Verb ROIs Old > Young	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)
Frontal					*Frontal*				
Pre/Postcentral gyrus	759	R BA 4, 6, 43, 3/1/2	-53, 11, 31	5.05	IFG, MFG	154	R BA 44, 9	-28, -12, 28	4.93
					SFG, MFG	84	R BA 8	-19, -18, 40	5.00
Precentral gyrus	118	R BA 6	-62, 4, 12	5.31					
Posterior perisylvian					*Posterior perisylvian*				
Angular gyrus	656	L BA 39	24, 59, 32	5.94	Angular gyrus	781	L BA 39	24, 58, 33	5.60
MTG	83	L BA 37, 21	55, 51, -4	4.42					
SMG	92	R BA 40	-57, 30, 47	4.78					
	85	R BA 40	-63, 33, 41	4.38					
Other regions					*Other regions*				
Superior parietal	112	L BA 7	24, 68, 43	4.44	Superior parietal	170	L BA 7	25, 68, 43	4.48
Postcentral gyrus	94	L BA 40	62, 21, 24	4.50					

Abbreviations: ROI = Region of interest. SD = Standard deviation. BA = Brodmann's area. L = Left. R = Right. IFG = Inferior frontal gyrus. MFG = Middle frontal gyrus. Medial = Medial frontal cortex. STG = Superior temporal gyrus. MTG = Middle temporal gyrus. SMG = Supramarginal gyrus. Cluster size > 78 microliters, p<.001.

Table 8-3. Correlations between fMRI word generation active ROIs and word generation performance.

Accuracy	Noun Generation		Verb Generation	
	L angular gyrus	R precentral/postcentral gyrus	L angular gyrus	R inferior/middle frontal gyrus
Young	.15	.22	.34	.08
	p = .59	p = .42	p = .22	p = .79
Old	.41	-.29	-.26	.06
	p = .14	p = .32	p = .37	p = .85

L = Left. R = Right. * = p<.05.

Table 8-4. FMRI region of interest (ROI) area under the curve time course data. Young t-test comparisons for noun and verb generation versus baseline.

Noun ROIs	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)	Verb ROIs	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)
Frontal					*Frontal*				
IFG, insula	2215	L BA 45, 47, 44	35, -18, -2	8.23	IFG, insula	509	L BA 45	29, -31, 7	6.29
						370	L BA 47, 45	35, -19, -1	5.82
	742	R BA 45, 47	-45, -19, -1	6.82		570	R BA 47, 45	-44, -20, -1	6.72
IFG, MFG	257	R BA 45, 46	-49, -28, 17	6.12	IFG, MFG	3287	L BA 9, 46, 45, 44	35, -25, 24	8.51
MFG	1727	L BA 9, 46	41, -11, 28	6.48					
Medial	3802	B BA 6, 8, 32	5, -15, 37	9.45	Medial	3716	B BA 6, 8, 32	5, -16, 37	8.54
Subcortical					*Subcortical*				
Caudate, striatal bridges	229	L	15, 1, 15	5.27	Caudate, striatal bridges	446	L	14, 0, 17	7.37
Putamen	168	R	-26, -11, 7	6.72	Putamen, striatal bridges, insula	526	R	-22, -10, 16	6.39
Posterior perisylvian					*Posterior perisylvian*				
STG, MTG	354	L BA 22, 21	57, 43, 5	5.76	STG, MTG	799	L BA 22, 21	57, 45, 6	7.43
					Inferior parietal, SMG	90	L BA 40	31, 44, 40	5.02

Abbreviations: ROI = Region of interest. SD = Standard deviation. BA = Brodmann's area. L = Left. R = Right. B = Bilateral. IFG = Inferior frontal gyrus. MFG = Middle frontal gyrus. Medial = Medial frontal cortex. STG = Superior temporal gyrus. MTG = Middle temporal gyrus. SMG = Supramarginal gyrus. Cluster size > 78 microliters, p<.001.

Table 8-5. FMRI region of interest (ROI) area under the curve time course data. Old t-test comparisons for noun and verb generation versus baseline.

Noun ROIs	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)	Verb ROIs	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)
Frontal					*Frontal*				
IFG, MFG, SFG, precentral	6603	L BA 44, 45, 6, 9	46, -3, 28	7.75	IFG, MFG, precentral	5927	L BA 44, 45, 6, 9	42, -2, 19	8.22
IFG, insula	3264	L BA 47, 45, 44	40, -19, -2	7.31	IFG, insula	1553	L BA 47, 45	40, -21, -5	7.28
						105	R BA 45	-51, -30, 14	5.38
	120	R BA 45	-52, -29, 13	5.32		96	R BA 45	-29, -9, 25	5.85
IFG, precentral	608	R BA 44, 6	-59, -12, 3	6.26	IFG, precentral	467	R BA 44, 6	-60, -12, 3	6.02
MFG, precentral	417	R BA 6	-49, -3, 43	6.53	MFG, precentral	112	L BA 6	23, -8, 49	5.45
						262	R BA 6	-49, -2, 44	6.45
						171	R BA 6	-28, 6, 50	6.25
MFG	706	L BA 9	40, -24, 32	6.99	IFG, MFG	1820	L BA 45, 9, 46	42, -24, 30	6.95
	661	L BA 10	40, -43, 4	7.31	MFG	287	L BA 46, 10	41, -44, 5	5.95
	337	L BA 10	30, -56, 22	6.57		468	L BA 10	30, -56, 21	7.14
	247	R BA 6	-27, -9, 45	6.58		118	R BA 9	-47, -13, 30	5.21
	85	R BA 6	-39, 0, 55	6.12		88	R BA 9	-45, -37, 30	6.10
					MFG, SFG, Precentral	1437	L BA 6, 4	32, 3, 56	6.67
Medial	6466	B BA 6, 8, 32	-14, -18, 40	9.42	Medial	8056	B BA 6, 8, 32	0, -23, 38	8.28
	117	L BA 6	1, 25, 70	5.23		139	L BA 6	1, 25, 70	5.98
Subcortical					*Subcortical*				
Caudate, striatal bridges	269	L	18, -6, 5	6.00	Caudate	269	L	13, 6, 17	6.52
	168	L	13, 7, 17	5.78					
Pulvinar	177	L	23, 29, 10	12.13	Pulvinar	113	L	23, 28, 10	10.16
Putamen, striatal bridges	88	R	-23, -5, 10	5.82					
Posterior perisylvian					*Posterior perisylvian*				
SMG, Angular, SPL, IPL, Postcentral	10247	L BA 40, 39, 7, 2	25, 55, 33	9.06	SMG, Angular, SPL, IPL	7787	L BA 40, 39, 7	21, 51, 30	9.49
STG, MTG, ITG	1294	L BA 22, 21, 20	51, 46, 9	6.25	STG, MTG, fusiform, parahippocampal	7976	L BA 22, 21, 20, 37, 19	13, 44, -17	9.29
STG	184	L BA 22	56, 34, 11	5.91					

Table 8-5. Continued

Noun ROIs	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)	Verb ROIs	Volume (mm^3)	BA/ subregion	Mean Intensity (x,y,z)	Peak Intensity (t-value)
STG, MTG	798	R BA 22, 21	-48, 41, 2	6.60	STG, MTG	400	R BA 22, 21	-50, 39, -2	6.89
Angular gyrus, SPL	1705	R BA 39, 7	-33, 62, 37	8.97	Angular gyrus, IPL, SPL	1130	R BA 39, 40, 7	-36, 64, 41	8.39
SMG, postcentral	881	R BA 40	-49, 40, 48	8.39	SMG, IPL, postcentral	493	R BA 40	-49, 40, 47	6.23
Other areas					*Other areas*				
Postcentral	467	L BA 40	63, 17, 16	7.93	Postcentral	303	L BA 43, 2	57, 19, 18	6.93
	164	L BA 3/1/2	50, 20, 34	5.96		191	L BA 43	54, 21, 36	6.30
	137	R BA 3/1/2	-40, 22, 50	6.64		82	L BA 43	54, 8, 17	4.89
						145	R BA 3/1/2	-40, 22, 50	6.42

Abbreviations: ROI = Region of interest. SD = Standard deviation. BA = Brodmann's area. L = Left. R = Right. B = Bilateral. IFG = Inferior frontal gyrus. MFG = Middle frontal gyrus. SFG = Superior frontal gyrus. Medial = Medial frontal cortex. SFG = Superior frontal gyrus. STG = Superior temporal gyrus. MTG = Middle temporal gyrus. ITG =Inferior temporal gyrus. SMG = Supramarginal gyrus. SPL = Superior parietal lobe. IPL = Inferior parietal lobe. Cluster size > 78 microliters, $p<.001$.

Table 8-6. Anatomy-based region of interest (ROI) area under the curve time course data. Young versus old repeated measures analysis of variance (ANOVA) data for lateral and medial frontal ROIs during noun and verb generation.

ROI/Condition	Group	Mean (SD)	t-test	p-value	ROI/Condition	Group	Mean (SD)	t-test	p-value
L IFG Noun	Young	3.41 (2.48)	t (1,28) = -0.25	p = 0.80	R IFG Noun	Young	0.99 (2.17)	t (1,28) = 0.28	p = 0.78
	Old	3.69 (3.36)				Old	0.78 (1.88)		
Wilks' Lambda		0.45	F (1,12) = 1.70	p = 0.15	Wilks' Lambda		0.35	F (1,12) = 2.59	p = 0.036*
L IFG Verb	Young	3.75 (2.85)	t (1,28) = -0.18	p = 0.86	R IFG Verb	Young	0.88 (2.12)	t (1,28) = 0.05	p = 0.96
	Old	3.95 (3.23)				Old	0.84 (2.02)		
Wilks' Lambda		0.48	F (1,12) = 1.52	p = 0.21	Wilks' Lambda		0.36	F (1,12) = 2.51	p = 0.04*
L MFG Noun	Young	2.22 (4.32)	t (1,28) = -0.79	p = 0.44	R MFG Noun	Young	0.58 (1.87)	t (1,28) =-1.16	p = 0.26
	Old	3.19 (1.99)				Old	1.34 (1.74)		
Wilks' Lambda		0.47	F (1,12) = 1.62	p = 0.18	Wilks' Lambda		0.30	F (1,12) = 3.29	p = 0.013*
L MFG Verb	Young	2.28 (4.25)	t (1,28) = -0.72	p = 0.48	R MFG Verb	Young	0.36 (2.0)	t (1,28) = -1.31	p = 0.20
	Old	3.14 (1.84)				Old	1.25 (1.75)		
Wilks' Lambda		0.56	F (1,12) = 1.11	p = 0.41	Wilks' Lambda		0.42	F (1,12) = 1.94	p = 0.10
L Medial Noun	Young	0.31 (1.29)	t (1,28) = 0.39	p = 0.70	R Medial Noun	Young	-0.25 (2.19)	t (1,28) = -0.17	p = 0.87
	Old	0.08 (2.02)				Old	-0.13 (1.59)		
Wilks' Lambda		0.64	F (1,12) = 0.80	p = 0.65	Wilks' Lambda		0.32	F (1,12) = 2.95	p = 0.02*
L Medial Verb	Young	0.28 (1.50)	t (1,28) = 0.50	p = 0.62	R Medial Verb	Young	-0.31 (2.79)	t (1,28) = -0.07	p = 0.94
	Old	-0.03 (1.78)				Old	-0.26 (1.54)		
Wilks' Lambda		0.53	F (1,12) = 1.24	p = 0.33	Wilks' Lambda		0.60	F (1,12) = 0.96	p = 0.52

Abbreviations: ROI = Region of interest. SD = Standard deviation. L = Left. R = Right. IFG = Inferior frontal gyrus. MFG = Middle frontal gyrus. Medial = Medial frontal region. * = p<.05. ** = p<.0125.

Table 8-7. Anatomy-based region of interest (ROI) area under the curve time course data. Young versus old repeated measures analysis of variance (ANOVA) data for subcortical ROIs during noun and verb generation.

ROI/Condition	Group	Mean (SD)	t-test	p-value	ROI/Condition	Group	Mean (SD)	t-test	p-value
L STN Noun	Young	0.87 (2.42)	t (1,28) = -1.36	p = 0.19	R STN Noun	Young	0.75 (1.74)	t (1,28) = -1.08	p = 0.29
	Old	2.06 (2.37)				Old	1.59 (2.47)		
Wilks' Lambda		0.27	F (1,12) = 3.78	p = 0.006**	Wilks' Lambda		0.24	F (1,12) = 4.56	p = 0.002**
L STN Verb	Young	0.54 (2.29)	t (1,28) = -2.02	p = 0.05*	R STN Verb	Young	0.63 (1.58)	t (1,28) = -1.02	p = 0.32
	Old	2.42 (2.78)				Old	1.46 (2.71)		
Wilks' Lambda		0.42	F (1,12) = 1.99	p = 0.10	Wilks' Lambda		0.38	F (1,12) = 2.34	p = 0.05*
L Caudate Noun	Young	1.33 (1.50)	t (1,28) = 0.47	p = 0.64	R Caudate Noun	Young	0.44 (1.16)	t (1,28) = 0.66	p = 0.52
	Old	1.08 (1.41)				Old	0.17 (1.08)		
Wilks' Lambda		0.23	F (1,12) = 4.82	p = 0.002**	Wilks' Lambda		0.36	F (1,12) = 2.54	p = 0.04*
L Caudate Verb	Young	1.30 (1.85)	t (1,28) = 0.42	p = 0.68	R Caudate Verb	Young	0.42 (1.31)	t (1,28) = 0.31	p = 0.76
	Old	1.05 (1.38)				Old	0.29 (0.97)		
Wilks' Lambda		0.58	F (1,12) = 1.03	p = 0.46	Wilks' Lambda		0.43	F (1,12) = 1.87	p = 0.12
L GP Noun	Young	0.86 (1.56)	t (1,28) = -0.63	p = 0.54	R GP Noun	Young	0.80 (1.26)	t (1,28) = -0.66	p = 0.51
	Old	1.26 (1.89)				Old	1.16 (1.71)		
Wilks' Lambda		0.48	F (1,12) = 1.57	p = 0.19	Wilks' Lambda		0.41	F (1,12) = 2.05	p = 0.09
L GP Verb	Young	1.07 (1.72)	t (1,28) = -0.32	p = 0.75	R GP Verb	Young	0.51 (1.42)	t (1,28) = -1.14	p = 0.26
	Old	1.31 (2.48)				Old	1.16 (1.69)		
Wilks' Lambda		0.42	F (1,12) = 1.96	p = 0.10	Wilks' Lambda		0.54	F (1,12) = 1.22	p = 0.34
L Thalamus Noun	Young	0.90 (1.38)	t (1,28) = -0.78	p = 0.44	R Thalamus Noun	Young	0.83 (1.45)	t (1,28) = -0.11	p = 0.91
	Old	1.26 (1.17)				Old	0.92 (2.61)		
Wilks' Lambda		0.47	F (1,12) = 1.58	p = 0.19	Wilks' Lambda		0.49	F (1,12) = 1.48	p = 0.23
L Thalamus Verb	Young	0.89 (1.32)	t (1,28) = -1.02	p = 0.32	R Thalamus Verb	Young	0.70 (1.52)	t (1,28) = -0.11	p = 0.92
	Old	1.41 (1.48)				Old	0.78 (2.69)		
Wilks' Lambda		0.51	F (1,12) = 1.37	p = 0.27	Wilks' Lambda		0.32	F (1,12) = 3.01	p = 0.02*

Abbreviations: ROI = Region of interest. SD = Standard deviation. L = Left. R = Right. STN = Subthalamic nucleus. GP=Globus pallidus.
* = p<.05. ** = p<.0125.

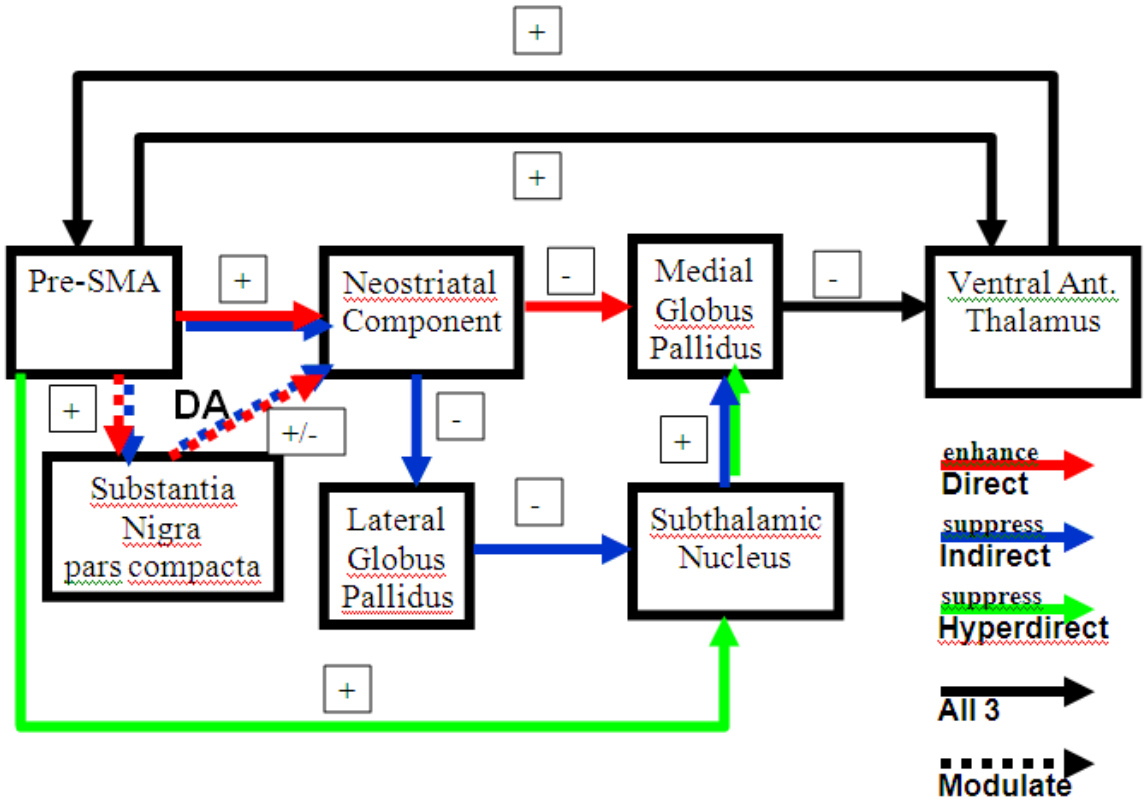


Figure 8-1. Schematic diagram of pre–SMA–basal ganglia loop (Crosson, Benjamin, & Levy, 2007).

Direction of pathways between structures is indicated by the arrows. Reciprocated connections are indicated by separate arrows. The pathway for the "direct loop" is shown with red lines, the pathway for the "indirect loop" is shown with blue lines, and the pathway for the "hyperdirect loop" is shown with green lines. Positive signs (+) indicate excitatory effects of the pathway and negative signs (-) indicate inhibitory effects of the pathway. The neostriatal component of the loop probably consists of striatal gray bridges, but also may include the caudate nucleus or putamen on either side of the capsule (Inase et al., 1999). Note that dopaminergic projections from the substantia nigra pars compacta to the neostriatum have both excitatory and inhibitory effects, depending upon the target neurons (Gerfen, 1992).

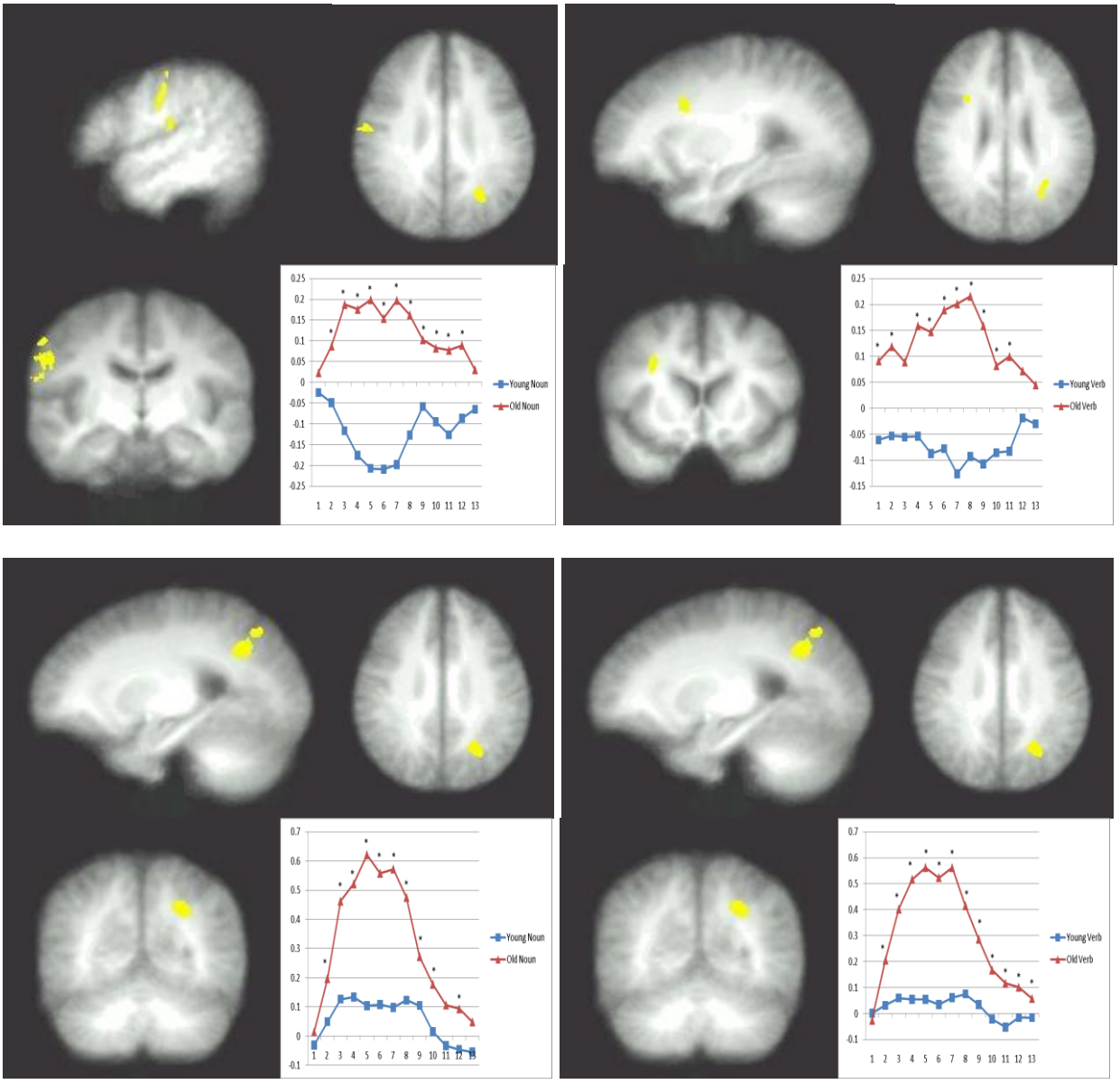
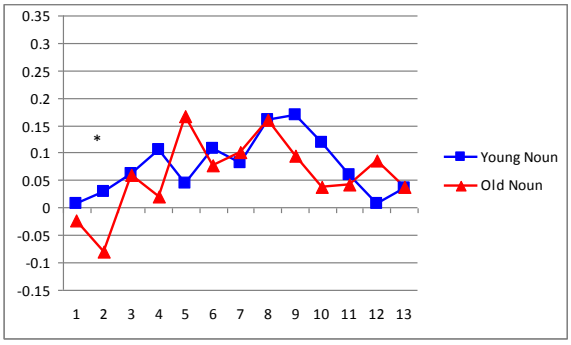


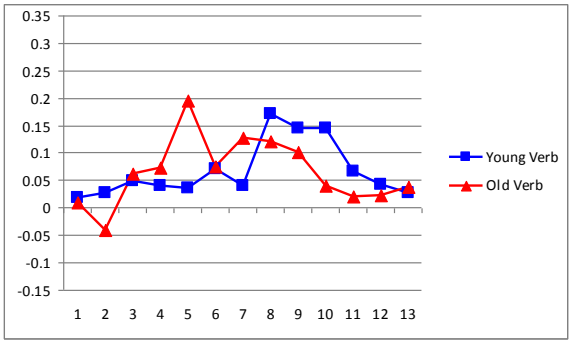
Figure 8-2. Functional activity during noun and verb generation for young versus old adults.

Top left: right precentral/postcentral gyrus during noun condition. Top right: right inferior frontal gyrus during verb condition. Bottom left: left angular gyrus during noun condition. Bottom right: left angular gyrus during verb condition. Sagittal, axial, and coronal views of the regions of interest (ROIs) with respective regions of interest time course data for fRMI area under the curve. Cluster size > 100 microliters; $p<.001$. * = significant between-group time course difference at $p\leq.01$.

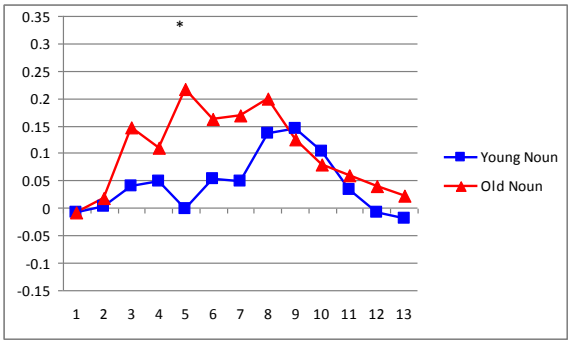
Right Inferior Frontal: Noun



Right Inferior Frontal: Verb



Right Middle Frontal: Noun



Right Medial Frontal: Noun

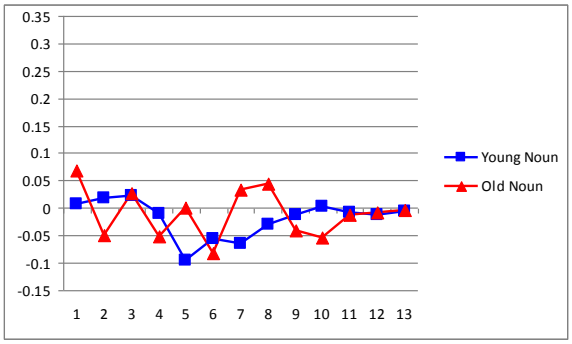


Figure 8-3. Impulse response function time course data for lateral and medial frontal ROIs.

Repeated measures ANOVA (group x 13 timepoints). $p<.05$.

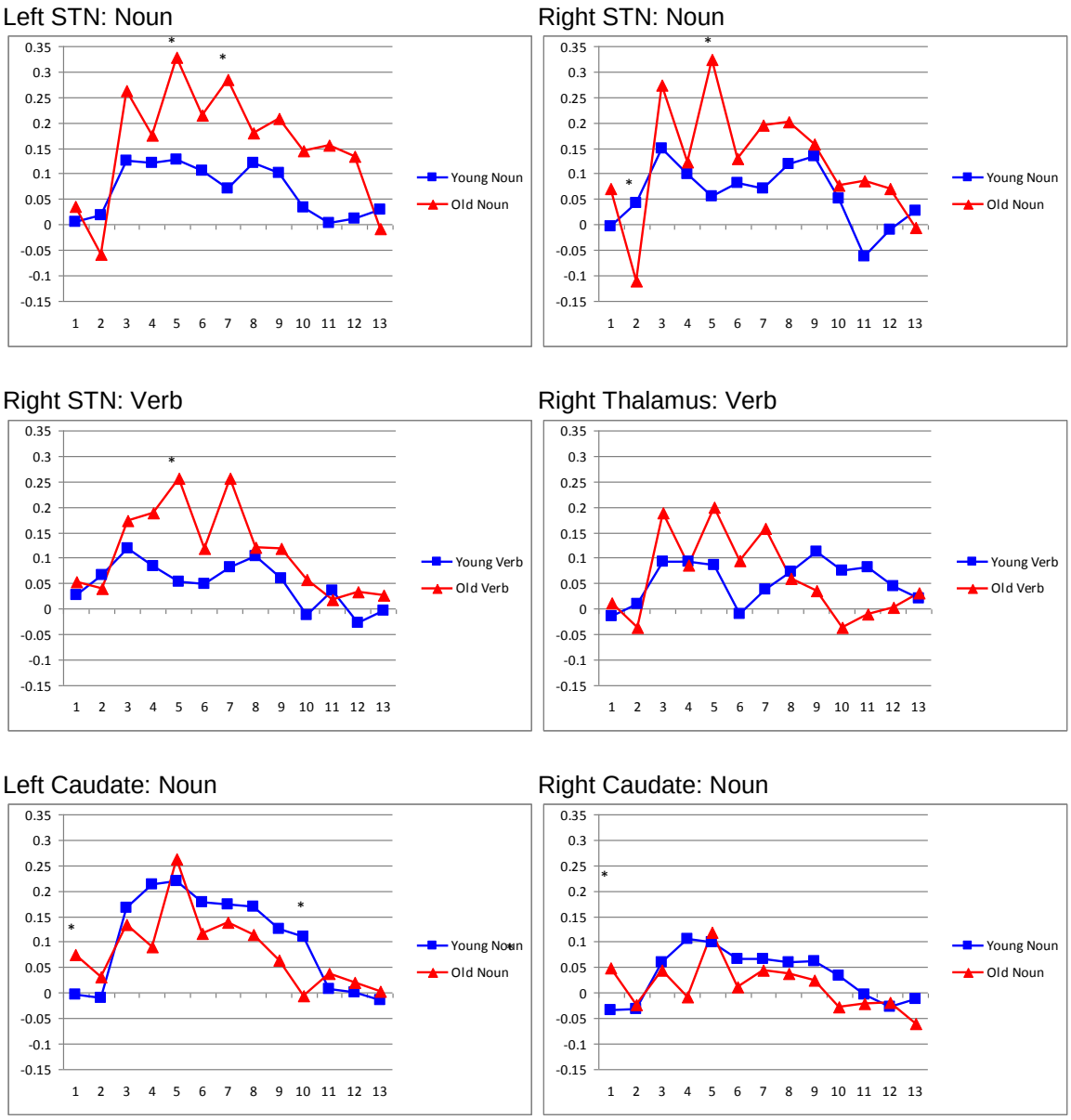


Figure 8-4. Impulse response function time course data for subcortical ROIs.

Repeated measures ANOVA (group x 13 timepoints). Left caudate, left STN, and right STN noun condition significant at p<.0125; other ROIs significant at p<.05.

APPENDIX
NOUN AND VERB GENERATION STIMULI

Table A-1. Noun and verb generation stimuli

Noun Living	Frequency	F & K		Noun Nonliving	Frequency	F & K	Verb Human	Frequency	F & K	Verb Nonhuman	Frequency	F & K
monkey		H	275	gun		H	142	reading		H	274	rolling		H	88
snake		H	70	knife		H	86	painting		H	95	flowing		H	40
cat		H	42	cup		H	58	laughing		H	89	sinking		H	40
corn		H	38	pencil		H	38	cooking		H	50	melting		H	32
fish		H	33	fan		H	34	whispering		H	31	digging		H	32
potato		M	30	pitcher		M	29	waving		M	30	boiling		M	27
sheep		M	24	lock		M	28	arresting		M	27	rotating		M	21
lemon		M	16	needle		M	21	smoking		M	26	nesting		M	20
eagle		M	12	fork		M	20	celebrating		M	25	popping		M	17
bee		M	27	thread		M	20	carving		M	23	blooming		M	17
lion		M	26	arrow		M	20	wrapping		M	23	flooding		M	15
peas		M	24	ladder		M	19	shaving		M	23	raining		M	14
mouse		M	20	basket		M	19	whistling		M	21	thundering		M	14
onion		M	19	axe		M	19	winking		M	18	dripping		M	14
elephant		M	18	pen		M	18	sewing		M	18	roaring		M	13
rabbit		M	16	stove		M	17	knitting		M	18	buzzing		M	13
apple		M	15	razor		M	15	skipping		M	17	snowing		M	12
orange		M	15	ruler		M	13	peeling		M	14	erupting		M	11
deer		M	13	plow		M	12	typing		M	12	grazing		M	9
pineapple		M	9	compass		M	12	mopping		M	9	soaring		M	9
turtle		M	9	umbrella		M	11	clapping		M	9	sprouting		L	8
pear		L	8	microphone		L	8	ironing		L	8	hatching		L	7
tomato		L	7	rake		L	8	coughing		L	8	thawing		L	6
duck		L	6	saw		L	8	vacuuming		L	6	freezing		L	6
carrot		L	5	shovel		L	8	twirling		L	6	howling		L	5
banana		L	5	spoon		L	6	buckling		L	6	swaying		L	5
celery		L	4	hammer		L	6	cheering		L	6	ticking		L	5
turkey		L	4	hook		L	5	raking		L	6	overflowing		L	4
mushroom		L	4	easel		L	5	erasing		L	5	burrowing		L	4
alligator		L	4	leash		L	4	combing		L	5	wagging		L	4
butterfly		L	3	cannon		L	4	scooping		L	5	wilting		L	3
spinach		L	2	mop		L	3	hammering		L	4	pecking		L	3

Table A-1. Continued

Noun Living	Frequency	F & K		Noun Nonliving	Frequency	F & K	Verb Human	Frequency	F & K	Verb Nonhuman	Frequency	F & K
pumpkin		L	2	corkscrew	L	3	boxing	L	4	clucking	L	3
frog		L	2	kettle	L	3	saluting	L	4	galloping	L	3
spider		L	2	pitchfork	L	2	wrestling	L	3	hibernating	L	2
watermelon		L	1	wrench	L	1	wringing	L	3	vibrating	L	2
broccoli		L	1	ladle	L	1	skiing	L	3	gusting	L	2
anteater		L	1	scissors	L	1	dabbing	L	3	migrating	L	1
lobster		L	1	hinge	L	1	skating	L	3	deflating	L	1
porcupine		L	1	blender	L	1	juggling	L	2	evaporating	L	1
squirrel		L	1	hoe	L	1	zipping	L	2	sleeting	L	1
zebra		L	1	syringe	L	1	golfing	L	1	croaking	L	1
whale		L	0	pliers	L	1	kneading	L	1	barking	L	1
giraffe		L	0	dishwasher	L	1	dribbling	L	1	pollinating	L	0
lettuce		L	0	screwdriver	L	0	curtseying	L	1	purring	L	0
peanut		L	0	toaster	L	0	surfing	L	0	hissing	L	0
penguin		L	0	stapler	L	0	parachuting	L	0	snarling	L	0
scorpion		L	0	spatula	L	0	sunbathing	L	0	waddling	L	0

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Michelle Benjamin graduated from DePaul University with a bachelor's degree in psychology. Prior to graduate school, Michelle worked as a research assistant at the Wisconsin Early Autism Project in Madison, Wisconsin where she was involved in studies evaluating treatment outcome effects for a behavioral modification treatment program for children diagnosed with autism and other pervasive developmental disorders. Michelle then went on to work as a research assistant for the Department of Psychiatry at the University of Iowa. At the University of Iowa, she was involved in research evaluating decisional capacity in schizophrenia, cognitive and psychiatric change in Huntington's disease, and the cognitive effects of atherosclerotic vascular disease.

Michelle began her doctoral training in the Department of Clinical and Health Psychology at the University of Florida in 2002 with a concentration in the area of neuropsychology. During her early graduate studies, Michelle pursued research interests in pediatric neuropsychology in the area of pediatric traumatic brain injury. She received her Master of Science degree in clinical psychology in 2004 from the University of Florida. During her graduate studies, Michelle pursued interests in subcortical functions and language through involvement in various research projects investigating healthy and impaired language functions using functional magnetic resonance imaging (fMRI). Michelle completed an internship in clinical psychology at the University of Alabama at Birmingham where she continued to develop her knowledge of clinical neuropsychology. She is completing her postdoctoral studies at the University of Alabama at Birmingham in the Department of Psychiatry and Behavioral Neurobiology.