NEURAL CORRELATES OF SEMANTIC INHIBITION IN OLDER AND YOUNGER ADULTS

By

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To my father Michael Jonathan Levy for the strength and balance that comes from knowing that every day counts and it’s not important how long you live but who you touch during your life

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ACC	Anterior Cingulate Cortex
aMCI	Amnestic Mild Cognitive Impairment
AUC	Area Under the Curve
BOLD	Blood Oxygenation Level Dependent
DA	Dopamine
DBS	Deep Brain Stimulation
DLPFC	Dorsolateral Prefrontal Cortex
dPM	Dorsal Premotor Cortex
fMRI	Functional Magnetic Resonance Imaging
HAROLD	Hemispheric Symmetry Reduction in Older Adults
IFG	Inferior frontal gyrus
IFIS	Integrated Functional Imaging System
M1	Primary Motor Cortex
MMSE	Mini-Mental State Exam
MNI	Montreal Neurological Institute
PD	Parkinson's Disease
PET	Positron Emission Tomography
Pre-SMA	Pre-supplementary Motor Area
ROI	Region of Interest
RT	Reaction Time
rTMS	Repetitive Transcranial Magnetic Stimulation
SD	Standard Deviation
SOAs	Stimulus Onset Asynchronies
STN	Subthalamic Nucleus

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Neuroimaging and behavioral studies have indicated frontal cortical areas and the basal ganglia as playing key roles in modulating inhibitory processes (Castner et al., 2007). This study examines inhibitory language processes and age related changes through use of a sentence completion task similar to the Hayling test (Burgess & Shallice, 1997).

Old (n=15; Mean age=76) and young (n=15; mean age=23) healthy adults underwent a neuropsychological assessment and fMRI while performing a sentence completion task. Brain activity (i.e., fMRI) and behavioral responses (i.e., reaction time (RT), and response accuracy) while completing the sentence with an appropriate word (i.e. initiation task) was compared to performance when providing an unconnected response thought to require inhibition of the related words (i.e. inhibition task). Analysis involved both within group (Initiation vs. Inhibition task) and between group (Old vs. Young) comparisons.

Results of behavioral comparisons revealed that the old group performed significantly slower than the young group for the inhibition task although not for the initiation task and made significantly more errors than the young group during the

inhibition task demonstrating that the older participants had greater difficulty generating unrelated responses and inhibiting responses related to the sentences as compared to the young group.

Brain imaging results revealed frontal (DLPFC, SFG, OFC), parietal (precuneus, angular gyrus) and temporal (SMG) regions significantly associated with inhibition in the young group but no significant task differences in the older group. Further analysis revealed significant age related differences on both tasks thought to be the result of a combination of brain related changes with age and differences in the way the groups were performing the task. This pattern of performance suggests that the networks involved in inhibitory language tasks change with age though more research is needed to characterize these differences.

CHAPTER 1
INTRODUCTION

Changes in Frontal Lobe Function in Aging and Pathology

As the cohort of older adults in our society increases and the number of individuals surviving into old age continues to rise, research in aging has flourished. Differences between older and younger adult brains have been a focus of significant interest in the literature and led to further investigation as to what these differences may mean for behavioral performance and development across the lifespan. One area which has been functionally implicated across many cognitive domains is the frontal lobes. The literature has continued to provide evidence for differences in frontal lobe function in older adults as compared to younger adults. Specifically the phenomenon of hemispheric asymmetry reduction in older adults (HAROLD) states that while performing similar cognitive tasks, prefrontal activity tends to be less lateralized in older adults than in younger adults. The HAROLD model has been reported across domains of episodic memory, semantic memory, working memory, perception, and inhibitory control. In spite of the accumulation of evidence supporting this model, a debate remains as to whether these age-related hemispheric asymmetry reductions serve a compensatory function or whether they reflect difficulty in recruiting specialized neural mechanisms, possibly due to a reduction in inhibition of unrelated areas, referred to as dedifferentiation (Cabeza, 2002). Another important consideration in aging, is that although normal aging is not in itself pathological, there are aging related changes in brain structure and chemistry which bear some similarity to pathological conditions. For example, the dopamine (DA) system which is significantly damaged in Parkinson's

disease (PD), is also negatively affected in aging by what appears to be a significant and steady decline of brain dopamine levels with older age (Kaasinen & Rinne, 2002).

Over the last decade there has been a steady progression in our understanding of the many roles of the frontal lobes. This headway has been aided significantly by studies that comprehensively examined patients with focal frontal lesions. This research has led to improved knowledge of the anatomical and behavioral specificity within the frontal lobes (Stuss et al., 2002). The assumption is that individuals with damage to a particular region will show comparable impairments if the damaged region is involved in a specific function, even if additional surrounding tissue is also affected. Major neuro-anatomical areas have been differentiated through these studies including right and left dorsolateral frontal regions, and superior medial and inferior medial frontal regions. Neuropsychological assessments have demonstrated that when each of these areas was damaged, impairments in similar cognitive processes resulted. Specifically of interest to this study is that both the right dorsolateral frontal and the inferior medial frontal regions were found to be involved during tasks requiring response inhibition (Stuss et al., 2002).

Additional evidence from functional magnetic resonance imaging (fMRI) and repetitive transcranial magnetic stimulation (rTMS) have implicated similar areas in the right hemisphere (Chambers et al., 2007; Garavan, Ross, Murphy, Roche, & Stein, 2002; Kelly et al., 2004) during the performance of frontal inhibitory tasks. Chambers and colleagues (2007) cleverly dissociated the role of the right dorsal premotor cortex (dPM) in the execution of a task from the role of the right inferior frontal gyrus (IFG) in response inhibition. The task involved a flanker/stop-signal paradigm in which

participants were required to respond to the direction of a central arrow, flanked by either congruent or incongruent distracters, with the corresponding hand. The target was periodically interrupted by a stop signal which required them to cancel their response. When this task was performed following rTMS of the IFG or dPM they found that stimulation of the right, but not left, dPM was found to facilitate RT performance for both hands in all conditions regardless of the degree of competition involved. In contrast, stimulation of the right, but not left, IFG was associated with impairments in stop-signal inhibition but only when competition existed during response selection (i.e. Incongruent trials). These data seem to suggest that the right IFG is especially important for inhibition during the suppression of a competing response.

It has also been suggested that different neuroanatomical networks may underlie the process of response inhibition depending on the difficulty or speed of the task. One model proposed that a right hemisphere network involving the dorsolateral prefrontal and right inferior parietal cortices may be involved during an easier task requiring slower response times. However, more activity in the superior medial region, including the anterior cingulate cortex (ACC) and pre-supplementary motor area (pre-SMA), may be expected with increased response speed during a more difficult task (Garavan et al., 2002). This raises a question about the influence of the length of preparation time on the type of network recruited and the relationship between controlled and automatic processing. To address this issue, another model was proposed using fMRI and controlling for stimulus presentation rate and behavioral performance as well as manipulating response-stimulus intervals. Results demonstrated that during a faster go-no-go task there were significantly higher levels of activation in the right dorsolateral

prefrontal cortex (DLPFC), and left putamen, caudate, precuneus and fusiform gyrus. This may be due to the higher demand on response selection processes with little preparation time. In contrast, the slower condition evidenced greater activity in the anterior right superior and middle frontal gyri and left inferior parietal cortex, perhaps representing a more deliberate, controlled response selection and inhibitory process associated with the increased preparation time (Kelly et al., 2004).

Although task differences likely contributed to these conflicting results, the existence of two frontal networks, a right lateral frontal network and a right medial frontal network, seem apparent during motor inhibition tasks. The basal ganglia also seem to play an important role in these networks and will be discussed in more detail below.

The Role of the Basal Ganglia in Complex Language Functions

Most of the research on the basal ganglia has revolved around their role in movement. It is widely accepted that the basal ganglia play a subtle role in movement, not by driving the movement exactly, but by enhancing selected movements and suppressing competing movements. A similar concept can be applied to linguistic activities, such as word selection or syntax production. Evidence for the role of the basal ganglia in language is supported by the cortico-basal ganglia-thalamic loops that have been studied, the numerous connections found and proposed between the basal ganglia and frontal/pre-frontal cortical regions, the evidence of complex language deficits in individuals with basal ganglia damage, as well as increasing fMRI evidence of basal ganglia involvement in language tasks (Crosson, Benjamin, & Levy, 2007). Recent evidence from our laboratory has detailed connections between the Broca's area and the basal ganglia (Ford et al., unpublished).

Basal Ganglia Loops

The basal ganglia form a complex group of structures deep within the cerebral hemispheres that are thought to influence movement and cognition through their interactions with various cortical and thalamic regions (Alexander, DeLong, & Strick, 1986; Middleton & Strick, 2000). In general, frontal-striatal circuits originate in frontal cortical regions such as primary motor cortex, premotor cortex, supplementary and pre-supplementary motor areas, anterior cingulate cortex, dorsolateral prefrontal cortex, and orbitofrontal cortex. Each circuit operates in a closed-loop fashion, beginning and ending at the same target cortical region (Figure 1-1).

Each basal ganglia circuit can be decomposed into three separate loops (Nambu, Tokuno, & Takada, 2002; Nambu et al., 2000). Activity in the "direct loop" is thought to enhance selected actions and cognitions (Gerfen, 1992; Mink, 1996; Penney & Young, 1986). Activity in the "indirect loop" is thought to suppress actions or cognitions that compete with those selected. More recently, a "hyperdirect" loop has been described (Nambu et al., 2002, 2000). In this loop, unlike the direct and indirect loops, the cortical component projects directly to its subthalamic nucleus (STN), bypassing the striatum. Action in the hyperdirect loop is thought to have a suppressing effect on actions and cognitions.

Nambu and colleagues (2000) stimulated primary motor cortex (M1) in macaque monkeys and measured effects on the basal ganglia downstream in the medial globus pallidus. Although the exact time scale certainly does not apply to cognition, Crosson, Benjamin and Levy (2007) suggested the general sequence of events does. Activity in the medial globus pallidus indicates that after M1 stimulation there is an initial suppression of behavior/cognition followed by an intermediate enhancement of

behavior, finally followed by a late suppression of behavior. Nambu and colleagues (2002) suggested that the initial wave of suppression resets the system by allowing it to change ongoing behavior/cognitions to new ones. The intermediate wave of enhancement raises the probability of initiating selected behaviors/cognitions. Finally, the late wave of suppression decreases the probability of the occurrence of competing behaviors/cognitions.

Additional neurotransmitter influences occur from dopaminergic projections via the substantia nigra pars compacta to the striatal component of the frontal-striatal circuitry. While dopaminergic actions are less straightforward than the actions of neurotransmitters elsewhere in the frontal-striatal circuitry, dopamine is thought to influence both the direct and indirect basal ganglia pathways.

The rationale for outlining basal ganglia circuitry and neurotransmission is that a disease or injury at various points along this circuitry should display predictable neurocognitive deficits. Thus, certain disease states or brain injuries should theoretically produce problems with “enhancement” of certain cognitive functions through involvement of the direct basal ganglia circuitry, while others may produce dysfunction along the “suppression” continuum via involvement of the hyperdirect and/or indirect circuitry and related functions. An understanding of basal ganglia pathways is important in the context of this study as a primary goal is to better characterize inhibitory phenomena in the normal aging process in the hopes that this knowledge will inform our understanding of potential neuropathological processes and likely consequences.

Evidence of Complex Language Problems in Basal Ganglia Disorders

Semantic priming studies have commonly been used to examine subtle differences in language processes among patient groups and as a way of better

understanding the time course of language processing in healthy subjects. The idea that a person should respond faster to a lexical decision about a target when that target is preceded by a semantically related word (i.e., the prime), is based on the cognitive model of spread of activation in lexical and semantic networks. In this model, at the time the prime is activated, this activity will also begin to spread to nearby (i.e. related) nodes in the lexical and semantic networks. It follows that if the target is already somewhat activated a person should be able to respond to it faster than an unrelated word outside of the network that has not been primed (Chenery, Angwin, & Copland, 2008). The tricky part is determining the duration and timing of the effects of the semantic network. Some very clever experiments have provided us with a way to examine these effects.

In a study of direct (e.g., tiger-stripes) and indirect (e.g., lion-stripes) priming it was found that healthy controls showed faster RT to direct conditions than indirect conditions, which intuitively makes sense since the indirect condition would involve a more mediation by an intermediate node in the semantic network. Priming effects (i.e. faster RT to related than unrelated targets) were found at a short delay between prime and target as well as a longer delay. Interestingly, when healthy subjects were given L-Dopa prior to participation, their priming effects differed systematically compared to controls (Angwin et al., 2004; Kischka et al., 1996). Although direct and indirect priming effects were still found at the short delay between prime and target, priming effects disappeared more quickly than for controls not given L-Dopa, at the longer delay. These data suggest that DA modulates aspects of semantic activation possibly by reducing the spread of activation, effectively focusing activation (Kischka et al., 1996) or by speeding up the rate of decay of semantic activation thereby changing the time course of priming

effects(Angwin et al., 2004). In other words DA may facilitate selection of the salient stimulus initially, but due to the early facilitation, the spread of activation diminishes earlier than in the controls not administered L-Dopa.

These results provide valuable information about the effects of damage to the DA system. Angwin and colleagues (2005) also found that individuals with PD demonstrated a different pattern of priming across stimulus onset asynchronies (SOAs). In other words, how much time was allowed between the prime and the target affected whether or not the semantic network was primed. However, when they separated those with poor auditory comprehension from those with intact auditory comprehension, they found that the most significant differences in priming were in those with poor auditory comprehension suggesting that perhaps the language problems were due to slower processing speed caused by changes to the DA system.

Copland (2003) found that priming effects on a lexical ambiguity task with word pairs that had either dominant (bank-money) or subordinate (bank-river) meanings differed for controls as compared to those with PD, non-thalamic subcortical lesions and cortical lesions. All groups demonstrated priming effects for the dominant condition at both the short and long inter-stimulus-intervals (ISI). However, the controls demonstrated priming for the subordinate meaning only at the short ISI and no priming at the longer ISI. In comparison, the PD and non-thalamic subcortical lesion groups continued to demonstrate priming for both conditions at the long ISI suggesting a lack of normal suppression and implying damage to the indirect loop.

Crosson and colleagues (2007) suggested that these studies may elucidate the time course of basal ganglia activity contributing to cognition and specifically language

production and provide evidence for a cognitive model similar to the structure of the model proposed by Nambu and colleagues (2000) for movement. In this model, suppression via the hyperdirect pathway initially resets the system prior to initiating a new cognition, followed by enhancement of the selected cognition via the direct pathway and finally suppression of competing alternatives via the indirect pathway. It is the indirect pathway that likely plays an important role in the inhibitory processes that will be addressed below.

Inhibitory Mechanisms in Language

The lesion model teaches us the benefits of studying patients with focal damage in order to explore brain-behavior connections. Impairments in inhibitory processes are commonly observed in individuals with PD suggesting that disruption to the DA system affects one's ability to cope with interference. Deep brain stimulation (DBS) of the STN has recently become a common treatment for the debilitating motor symptoms in PD. While DBS has been shown to significantly improve motor impairments associated with PD, reports on its effects on cognitive processes have been more varied in their results. The majority of studies that have found deficits in inhibitory processing during STN stimulation using Stroop interference type tasks and reported delayed RTs or greater numbers of errors during STN stimulation as compared to preoperative or off stimulation conditions (Alegret et al., 2001; Moretti et al., 2003). These differential results suggest that the STN may be involved in inhibitory control through the modulation of basal ganglia-thalamocortical circuits. Therefore, to investigate the role of the basal ganglia in inhibitory processing, it is useful to first look at studies of individuals with PD who have undergone DBS of the STN.

Declines in verbal fluency performance have also commonly been reported following STN DBS providing further evidence for the role of basal ganglia-thalamocortical circuitry in modulation of lexical-semantic processes such as word or meaning retrieval. Verbal fluency tasks require two main cognitive processes: response initiation and suppression of the current response in order to generate a novel response (Bouquet, Bonnaud, & Gil, 2003; Burgess & Shallice, 1996). The declines in performance on both interference tasks and fluency tasks following STN DBS, provides additional support for the involvement of basal ganglia and associated circuitry in inhibitory language processes.

The Hayling Test

One test which allows for the differentiation between components of initiation and inhibition during verbal word generation is the Hayling test (Burgess & Shallice, 1996, 1997). The test consists of sentences read aloud in which the last word is missing. In part *A* of the test, the examinee is asked to respond as quickly as they can with a word that completes the sentence. In part *B*, they are asked to respond with a word that is completely unrelated to the sentence or the word which would complete the sentence.

Burgess and Shallice (1996) found that when this test was given to individuals with frontal lobe lesions and healthy controls, all groups demonstrated significantly longer RTs during part B as compared to part A. By subtracting RTs for section A for each individual from RTs for section B, one can compute a measure representative of the additional ‘thinking time’ necessary to produce a novel word instead of simply completing the sentence. This subtraction also allows for a removal of the potential confound of initiation problems during the task. Individuals with frontal lobe lesions were found to perform both parts of the test slower than the healthy individuals and patients

with lesions in other parts of the brain suggesting significant deficits in response initiation and inhibition. Additionally, those with frontal lesions made significantly more errors than the other groups.

When this same task was administered to individuals with PD following STN DBS, interesting performance differences were noted on versus off stimulation. Overall, the PD group had slower RTs than the control group on both tasks. However, when on and off stimulation conditions were compared separately, the PD group in the on stimulation condition was found to have significantly slower RTs than controls or the off stimulation group in task A suggesting response initiation problems related to STN stimulation. In contrast, the PD group in the on stimulation condition performed more like controls in task B and on the B-A measure, and only the those in the off stimulation condition demonstrated significantly slower RTs than controls (Castner et al., 2007). The use of the Hayling test allowed researchers to isolate inhibitory lexical-semantic mechanisms in PD and determine the modulatory effect of basal ganglia-thalamocortical circuits though observation of the effects of STN stimulation on task performance. These data seem to suggest that STN stimulation may increase response initiation problems but improve response inhibition in PD. The mechanisms by which STN stimulation work are still under considerable debate. However, one hypothesis is that the inhibition deficits in PD participants in the off stimulation condition are due to hyperactivity of the STN and disruptions of the indirect pathway leading to excessive inhibition (Castner et al., 2007). STN stimulation may serve to modulate this disruption in the indirect pathway leading to more normal inhibitory processes.

Initiation and inhibitory processes are considered “executive functions” generally associated with frontal lobe activity and have been shown to decline with normal aging while other, non-executive cognitive functions remain more stable (Bielak, Mansueti, Strauss, & Dixon, 2006). When norms on the Hayling test were collected from a typical aging population it was found that increasing age was associated with slower responding overall. However, this effect was greater for task B than A. The number of errors was also significantly affected by age with younger individuals providing fewer error responses than older participants (Bielak et al., 2006). Taken together, these data suggest two questions. First, what is the nature of the involvement of the neuroanatomical structures or networks implicated in inhibitory processing in PD? Second, how are these structures or networks affected by normal aging?

Use of Neuroimaging as a Measure of Inhibition

Only a few studies have used neuroimaging to examine the neuroanatomical networks involved in inhibitory language processes by administering a version of the Hayling test (Allen et al., 2008; Collette et al., 2001; Nathaniel-James & Frith, 2002; Nathaniel-James, Fletcher, & Frith, 1997). Positron emission tomography (PET) studies have reported that the Hayling test elicits activity in prefrontal and lateral temporal regions in the language network (Nathaniel-James et al., 1997) and that response initiation (i.e. task A) is associated with increased activity in the left IFG, left middle and superior temporal gyri and bilateral inferior parietal lobes. These are areas that have been implicated in storage and retrieval of semantic information. During response inhibition (i.e. task B) greater activity was found in areas associated with manipulation of information, planning and inhibitory control including the left dorsolateral and orbital prefrontal cortices (Collette et al., 2001; Nathaniel-James & Frith, 2002). Similarly, when

Allen and colleagues (2008) administered a version of the Hayling test during fMRI, they reported that response inhibition was associated with greater activity in the left prefrontal cortex including the dorsolateral and orbito-frontal regions, as well as the precuneus bilaterally as compared to response initiation. The current study aims to extend this line of research to determine how these networks, thought to be involved in inhibitory processes, may be affected by the aging process.

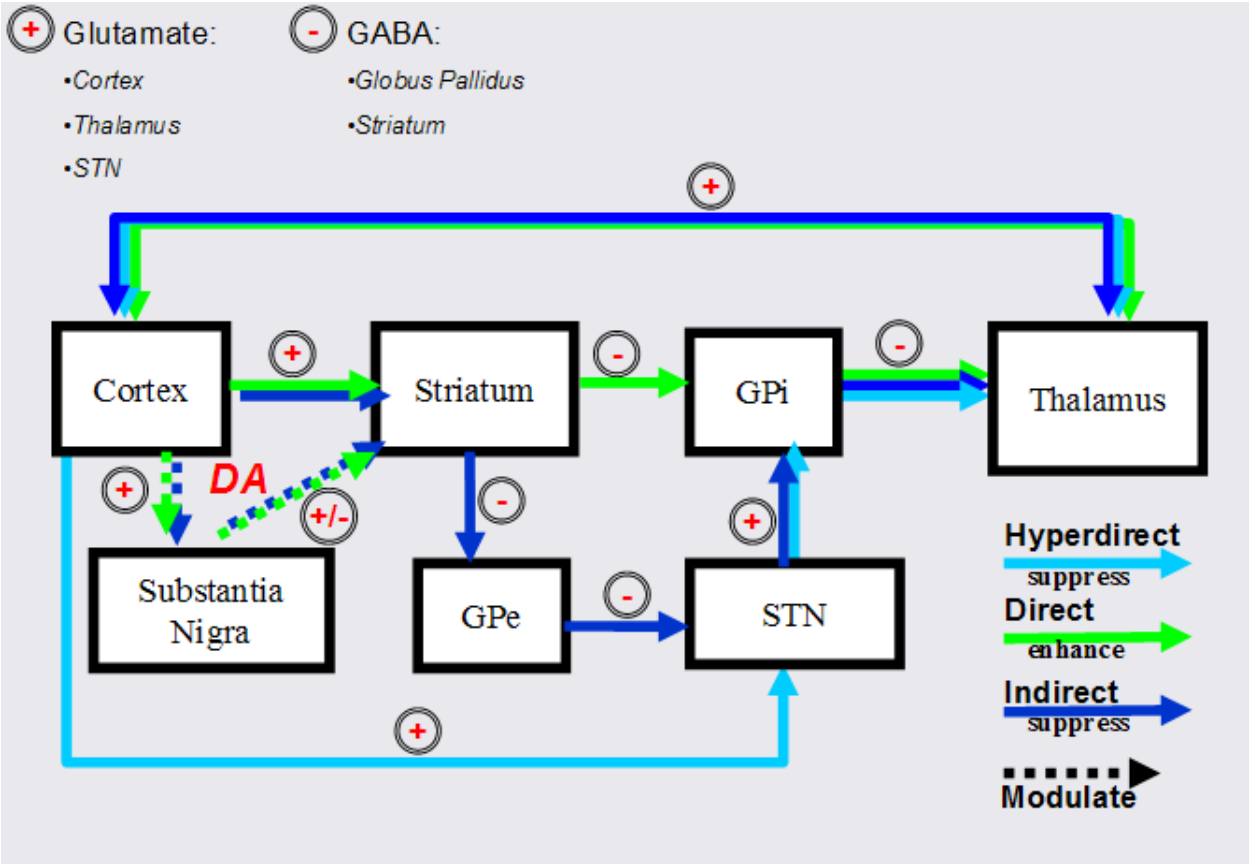

Figure 1-1. Cartoon of Basal Ganglia loops adapted from Crosson, Benjamin, & Levy (2007). GPi = Internal Globus Pallidus; GPe = External Globus Pallidus; STN = Subthalamic Nucleus; GABA = Gamma-Aminobutyric Acid; DA = Dopamine.

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CHAPTER 2
HYPOTHESES

Although previous studies have begun to investigate the neural correlates of inhibitory language processes by using versions of the Hayling test, the neuroanatomical networks are still not well understood. While behavioral studies have indicated that the basal ganglia play a key role in modulating these processes (Castner et al., 2007) the specific means of involvement has yet to be characterized using functional neuroimaging. The current study used fMRI and a version of the Hayling test (Burgess & Shallice, 1997) to investigate the effects of aging on the neural correlates of inhibitory semantic processing.

The present study is based on the premise that each component of the Hayling test is associated with a different set of cognitive processes (Figure 2-1). In order to successfully complete task A one needs to use language processes including those involved in reading (e.g., lexical-semantic, grammatical) as well as initiation of a response including retrieval of the correct word to complete the sentence and speech production of that word. In order to successfully complete task B, the same principles are involved, however, instead of simple retrieval of the word which completes the sentence, one must first inhibit the related words and instead produce a novel response which is unconnected to the sentence. Therefore, a subtraction of the processes (e.g., RT, fMRI activity) used to complete task A from those used to complete task B should reveal the unique processes used to produce inhibition. The current study was designed with the following hypotheses in mind:

Initiation versus Inhibition Hypothesis

Previous lesion and imaging studies lead us to believe that irrespective of age group we will find greater left frontal cortical activity in the dorsolateral, inferior medial frontal, and orbito-frontal regions (Allen et al., 2008; Stuss et al., 2002) during inhibitory processing as measured by a task B minus task A comparison to remove the contribution of initiation. Due to the nature of task B requiring inhibition of an expected response, and the proposed role of the STN in inhibitory processing through its modulation of the indirect loop, we also expect to find greater basal ganglia involvement, including STN and caudate nucleus, during performance of the inhibitory condition as compared to the initiation condition (Castner et al., 2007; Kelly et al., 2004).

Older versus Younger Hypothesis

During the response initiation + language processes condition (i.e., task A), which is a relatively simple sentence completion task, we do not expect to find significant group differences in brain activity, although we predict slower RTs for the older group as compared to the younger group based on the aging norms collected by Bielak and colleagues (2006).

In task B as compared to task A, we expect to find increased left DLPFC activity for the older group due to the increased effort involved in inhibiting the expected response. In contrast we expect decreased basal ganglia involvement in the older adult group due to the effects of age-dependent decline of brain dopamine levels (Elsinger et al., 2003; Kaasinen & Rinne, 2002). Although this effect is not pathological, it would also be consistent with reductions in dopamine activity in the basal ganglia for individuals with PD (Elsinger et al., 2003).

Relationship Between fMRI and Behavioral Performance

Although no subjects with pathological cognitive functions were included in this study, our hypotheses are based on the assumption that some differences exist between brain activity in younger and older adults during an inhibition task. Regardless of where in the brain these differences occur, it will be useful to characterize the relationship between regional brain activity and behavioral performance on the language task. Correlations will be calculated between average amount of activity in a given region of interest and behavioral performance differences as defined by reaction time and number of correct responses on the modified Hayling test. Findings of increased brain activity in older as compared to younger adults during word retrieval tasks (Cabeza, 2002; C. E. Wierenga, Benjamin, et al., 2008), even in the context of equivalent task performance, have provided evidence that heightened activity in some areas may be compensatory, while in others it may be nonbeneficial reduction in the ability to inhibit activity in regions of the brain unnecessary for task completion. The aging norms on the Hayling test (Bielak et al., 2006) demonstrated an association between older age and increased RT which is even slower on task B than A. These results suggest the need to determine whether there are brain regions which are associated with improved inhibition in older adults or conversely regions which are associated with poorer performance.

Using functionally defined anatomical regions of interest based on areas differentially active in the old and young groups, we expect to find a positive correlation between latency on task B and brain activity for the older adults (i.e., increased RT associated with greater activity). With regards to accuracy we expect the opposite

correlation such that a greater number of correct responses will be associated with less activity in those same regions of interest.

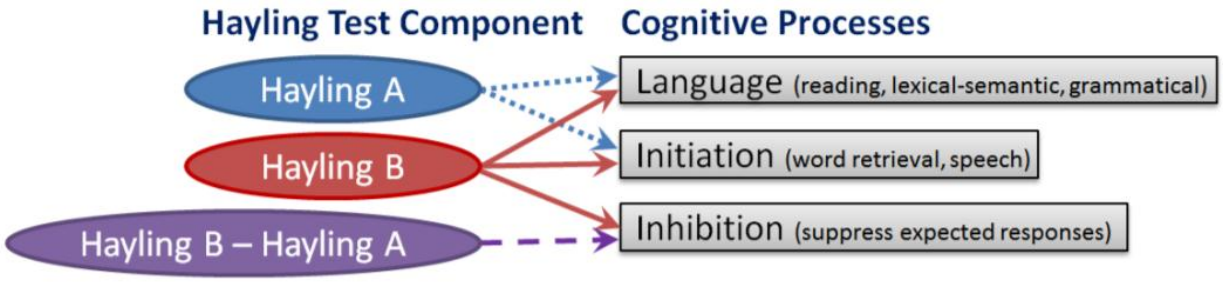


Figure 2-1. Model of Cognitive Processing Driving Activity in fMRI Voxels. The components of the Hayling test are used as measures of the cognitive processes thought to be involved in their completion. Task A involves various language processes as well as initiation of a response, while task B involves the former processes as well as inhibition. A subtraction of the processes involved in performing task A from those involved in task B is used as a measure of inhibition.

CHAPTER 3
METHODS

Participants

Sixteen (8 male, 8 female) neurologically normal young adults (age 18–35 years), and 16 (8 male, 8 female) neurologically normal older adults (age 65–80 years) participated in the study. One participant from the older group was excluded from final analyses due to a discovered brain abnormality and one was excluded from the younger group due to not following task instructions and responding before the cue, making the data unusable in the group analyses. Thus, each group included fifteen participants. Older and younger participants were matched for gender and level of education (Table 3-1) and there were no significant group differences on these variables. All participants were native English speakers recruited from the University of Florida faculty, staff, and students, the Malcom Randall VAMC and from the Gainesville, Florida community. All participants were strongly right-handed as determined by a score of greater than 50 on the Edinburgh Handedness Inventory (Oldfield, 1971). Potential participants were excluded if they reported any of the following medical problems: history of neurological disorder (e.g., stroke), or head trauma, dementia or Mild Cognitive Impairment, learning disability (e.g., dyslexia), psychiatric disorder (e.g., schizophrenia), substance abuse, or chronic medical conditions likely to impair cognition (e.g., cardiovascular disease, renal or hepatic failure). Since many prescription psychoactive medications may affect cognition, subjects on these classes of medications were also excluded. In addition, due to the fMRI component of the task, participants were excluded if they had metal in their body other than dental fillings and metal firmly anchored to bone or any other conditions contraindicated for MRI. Female participants were excluded if they were pregnant or

trying to become pregnant. On the day of the scan, participants were instructed to abstain from caffeine. 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 compensated for participation in the study.

Materials and Procedures

Dementia Screening

Prior to enrollment in the fMRI study, participants were administered a few brief cognitive tests in order to ascertain the presence of dementia or Mild Cognitive Impairment-amnestic type. As the goals of the study were to examine normal aging, it was decided to exclude those with Amnestic Mild Cognitive Impairment (aMCI), a precursor to pathological aging which has been indicated as a high-risk factor for the development of clinically probable Alzheimer's disease (Petersen et al., 2001). Criteria for aMCI include: a subjective memory complaint, preferably corroborated by an informant, impaired objective memory function for age and education, as compared to preserved general cognitive functioning, intact activities of daily living, and not meeting criteria for dementia (Petersen et al., 2001). Individuals who reported subjective memory complaints and who scored below 27 out of 30 on the Mini-Mental State Exam (MMSE) (Folstein et al., 1975) were excluded due to possible dementia. Individuals who obtained scores 1.5 SD or more below the age corrected norms on the Long-Delay Free Recall and Recognition Memory of the California Verbal Learning Test-II (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) were excluded due to possible aMCI.

fMRI Task Design

The Hayling test (Burgess & Shallice, 1997) was adapted for use in this fMRI experiment. The stimuli consisted of 60 sentence stems selected from those given by

Bloom and Fischler (1980, Appendix A). A primary consideration was the cloze probability (CP) for each sentence stem. CP is defined as the probability that a particular word will be used to complete a specific sentence in a given subject sample (Kutas & Hillyard, 1984). Highly constrained sentence stems lead to a high probability that a particular word will be used to complete it, while low constraint stems can be completed with a wide range of semantically appropriate words. Since responses for sentences with high CPs (CP> .6) involve a more restricted word choice pool, (e.g., Father carved the turkey with a ____ .) these sentence stems likely elicit less inhibitory processing during a response than those with moderate or low CPs. Sentence stems with low CPs (CP<.3) increase task difficulty due to the wider word choice pool (e.g. They went to see the famous ____ .) Although previous research (Allen et al., 2008) does not indicate significant differences in patterns of activity dependent on low versus high CPs, we chose to use only sentences with a moderate probability of one particular response (moderate-constraint sentences: CP between 0.3 and 0.6) in this study both to limit variability and balance the need to elicit inhibition with the desire to maintain the participant's ability to respond quickly and consistently to task items.

Sentence stems consisted of six or seven words. The 60 sentence stems were divided into two lists with equal CPs and numbers of 6 and 7 word sentence stems in each list. The MRC Psycholinguistic Database (Wilson, 1988) was used to match the critical word in each sentence for length, frequency, concreteness, and imageability and each list was balanced on these characteristics.

One list of sentences was used in the response initiation condition (i.e. task A) which required completion of the sentence with a congruent response (i.e., Jeff was

sent to bed without DINNER), while the other list was used in a response inhibition condition, in which an incongruent completion was required (i.e., The cup of tea felt very TELEPHONE). The 30 sentence stems in each of the two congruency conditions were arranged into 6 blocks containing 5 sentence stems each, for a total of 12 blocks which were alternated in an ABABABABABAB block design, (see Figure 3-1 for a schematic of the task design). The blocks were divided into 4 scanner runs which were either composed of one initiation and two inhibition blocks or one inhibition block and two initiation blocks. Stimulus presentation order was pseudo-randomized such that each participant received one of 8 different run sequences. The pseudorandomization, as opposed to true randomization, was used to preserve the alternating task design.

Prior to each block, a two second cue appeared on the screen, with either the word “GOOD” or “UNRELATED,” to inform the participant whether their task was to provide a congruent response or an incongruent response. Pilot data using a variety of cue words suggested that these were the most effective and least confusing cue words and did not appear to influence word choice in any way.

Sentence stems were presented visually in the MRI scanner by projection onto a screen positioned above the subject’s head using an Eloquence System (Invivo) designed to present stimuli and collect data in fMRI experiments and E-Prime version 1 software. Although auditory presentation was considered, variables including scanner noise, differences in reading speed as compared to auditory processing and synchronization of stimuli led to the decision to present stimuli visually. To control for inter-subject reading speed and reduce the potential for creating an accidental working memory task, each word in the sentence stem appeared on the screen one at a time at

an interval of 500 milliseconds (ms). Words appeared from left to right with all words in the sentence stem remaining on the screen after they were presented for the remainder of the trial. Participants were then cued to articulate their verbal response by the appearance of an underscored blank (e.g., _____) following the last word of the sentence stem which remained on the screen for a further 4 sec to allow for the subject's response. In order to align responses of the 6 word (3 second duration) and 7 word (3.5 second duration) sentences and line up the appearance of the blank with the scanner image acquisition (TR=2 seconds). A variable rest time preceded each item (either 500ms or 1000ms) so that the total stimulus presentation time for each item equaled 4 seconds.

Each functional run began with an initial 12 seconds of rest during which the participant was instructed to focus on a fixation cross in the center of the screen. Each trial lasted 8 seconds followed by a resting block consisting of a fixation point presented for a variable duration of either 10, 12, or 14 seconds to allow for the hemodynamic response to return to baseline prior to the start of the next trial. In total, each block lasted between 1 min and 40 seconds to 1 min and 44 seconds and each run (either one initiation and two inhibition blocks or the reverse) lasted 5 minutes and 28 seconds. Before scanning, participants received training on the task which emphasized that in the inhibition condition responses should not be semantically related to the preceding sentence stem. In the training phase, participants were presented with 7 novel sentence stems for response initiation and 7 for inhibition; which were not later used during scanning. Once inside the scanner, participants were given standardized instructions before each run reminding them of their task for both the initiation and inhibition blocks.

Brain Image Acquisition

Images were acquired on a 3 Tesla Phillips whole body scanner. Images were collected with an 8 channel SENSE radio frequency head coil at the McKnight Brain Institute at the University of Florida Functional images were obtained with a 1-shot gradient echo EPI scan: 24 cm FOV, 80×80 matrix, 3mm×3mm in-plane resolution, TR = 2000 ms, TE = 30 ms, flip angle = 80◦. 38, 3mm thick axial slices covering the whole-brain were acquired. A high-resolution T1-weighted 3D scan (TE = 3.69 ms; TR = 8.06 ms; FOV= 24 cm; matrix size = 240x240; 180 1.0mm slices) was obtained to provide anatomic reference. Head motion was minimized using foam padding.

Behavioral Data Analysis

Overt verbal responses were coded during the scan as well as digitally recorded for analysis of error rates and response times. A digital audio editor program, Audacity®,(Ash et al., 1999) was used to remove scanner noise interference in the digital recordings, and two raters reviewed the files to ensure correct documentation of responses, calculation of response times and coding of error types. Response times are defined as the duration between the presentation of the blank following the last word of the sentence stem and the onset of the participant's verbal response. Average RTs for each condition for each group were compared along with number and type of errors. Statistical comparisons were analyzed using PASW statistics 18, Release version 18.0.0. An error analyses based on the rater classification guide described by Burgess and Shallice (1996,Table 3-2) was conducted on responses to the inhibition task (task B) which divided errors into two main error types, Correct completions (C) meaning the participant was unable to inhibit as directed by the task instructions and provided a response which correctly completed the sentence and responses semantically related to

the correct response. These semantic responses were further broken down into 4 categories, a semantic opposite (SO), a word semantically related to the subject of the sentence (SA), a word semantically related to the correct response (SB) and a vague or ludicrous completion (SC). Responses were coded by two independent raters and differences were discussed until agreement could be reached.

Behavioral data were analyzed through two repeated measures ANOVAs. The effect of group and task on response latency was explored using RT as the dependent variable (DV), and the effect of group and task on accuracy was explored using the number of correct responses as the DV.

FMRI Data Analysis

FMRI data were analyzed and overlaid onto structural images with the Analysis of Functional Neuroimaging (AFNI) program from the National Institutes of Health (Cox, 1996). The first 6 images of all the functional runs were discarded to ensure attainment of steady state. To control for the effects of head motion, time series images were spatially registered in three-dimensional space. Images were visually inspected for gross artifacts and quality control procedures applied to the data to detect residual motion or susceptibility artifact. For each of the subjects, the 4 imaging runs for the FMRI task were detrended of low frequency signal drifts (Birn, Saad, & 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 5mm full-width at half-maximum. For each voxel, the observed fMRI intensity time-series was modeled as the convolution of the experimental stimulus vector (comprised of 30 initiation trials and 30 inhibition trials) and the estimated best-fit of the impulse response

during the 12 seconds following stimulus presentation, allowing the hemodynamic response to return to baseline.

Following coding of the behavioral data, incorrect items (e.g., task A items which did not complete the sentence and task B items which correctly completed the sentence) and missed items were removed from each subject's data so that only correct responses were included in the final analyses.

The area under the curve (AUC) of the deconvolved HDR was used as the dependent variable for analyses. 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 then warped to the co-ordinates of a standard brain in Montreal Neurological Institute (MNI) space and resampled at a $1mm^3$ resolution using FMRIB Software Library (FSL) version 4.1 tools (Smith et al., 2004). Warping individual brains into standard space is a method widely used as a technique for comparing individual subjects whose data naturally contains variability in size and location of major sulci and gyri and was acquired in slightly different coordinates. The standard brain used was one that has been created from an average of 152 MRI scans of normal control subjects.

Cluster thresholding was set at a predetermined cluster size using AFNI's 3dClustSim program which determined the minimum number of voxels necessary in a given cluster to achieve a family-wise error corrected alpha level of .05. For data in MNI (space with voxel size of 1mm x 1mm x 1mm, adjusted for 5 mm smoothing, and assuming a cluster type that requires that at least the corners of each voxel included are

touching the corner of another voxel in the cluster, an uncorrected p-value of .0001 requires a minimum cluster size of 215 voxels.

Three sets of fMRI statistical analyses were completed to explore the neural correlates of task, inhibition, and age using AFNI's 3dttest program. For each of these analyses average AUC of the HDR was the dependent variable. Within group, within task, voxel-wise one-sample Student's *t*-tests were used to examine the effect of task activity as compared to activity during the baseline resting condition. Within group, paired-samples t-tests were used to compare activity during task A to activity during task B in order to examine the effect of inhibition. Between group, independent-samples t-tests were used to explore the effect of age by comparing activity in the young group to that of the old group on each task condition. A fourth, correlational analysis explored the relationship between cerebral responses and behavioral performance (RT) using Spearman's rank correlation coefficient. For this analysis, group cluster reports generated by the regions of difference between the old and young groups were overlaid as masks on individual subject data using the AFNI program 3dMaskAve to determine the average level of activity within a given region of interest (ROI) for each subject. Correlations were performed between level of activity in each ROI and behavioral performance on the modified Hayling Test subjects performed while in the scanner.

Table 3-1. Participant Demographics

Group Means(SD)	N	M/F	Age	Education (years)	MMSE	CVLT-LDFR	CVLT-R
Young	15	8/7	23.3(3.8)	16(2.1)	29.4(1.2)	0.67(0.99)	-0.13(0.51)
Old	15	7/8	76.7(5.1)	15.8(2.9)	28.8(0.9)	0.5(0.88)	-0.06(1.14)

Notes: Demographic data summarized above includes only participants whose data was included in the final analyses. N = number of participants; M/F=male/female; CVLT-LDFR=CVLT-II long delay free recall z-score; CVLT-R=CVLT-II recognition z-score.

Table 3-2. Error characterization of task B responses based on the Burgess & Shallice's rater classification guide (1996).

	Error Type Description	Classification
1.	Does the word reasonably complete the sentence (i.e. it's a word you might give yourself if asked to provide a word that would fit at the end).	C
2.	Is the word an opposite of what you might expect as an answer?	SO
3.	Is the word obviously semantically connected to the subject of the sentence?	SA
4.	Is the word obviously semantically connected to the expected response?	SB
5.	Does the word vaguely fit at the end of the sentence, but in a way that makes the sense of the sentence ludicrous or is the word a slang semi-obscenity?	SC

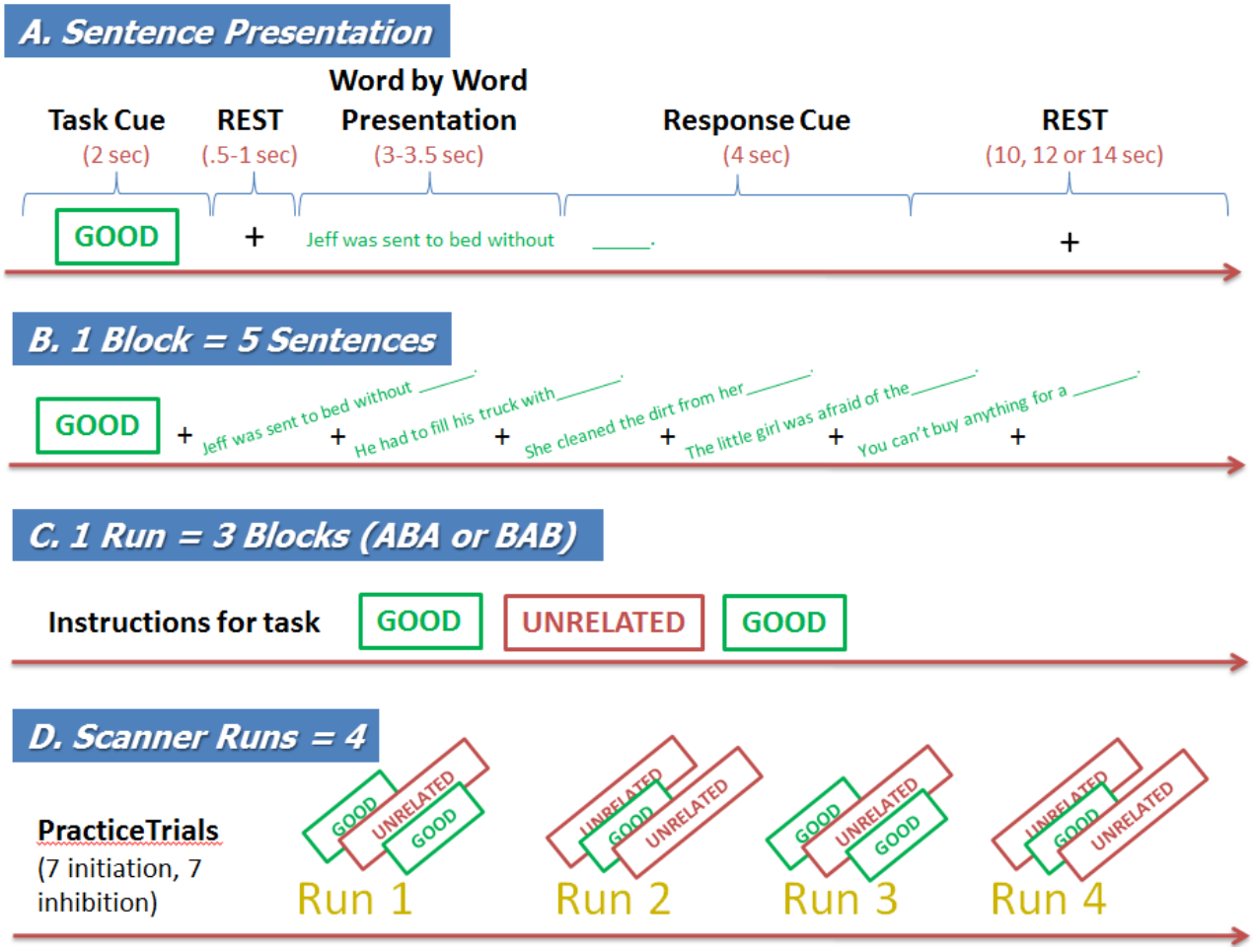


Figure 3-1. Schematic of task design. A) Components and timing of an individual item presentation. B) Sample block of 5 sentence stems. Prior to each block, participants were cues with either the word “GOOD” or “UNRELATED”. C) Sample scanner run which starts by reminding the participant of the task instructions and is followed by 3 blocks of 5 sentence stem. D) Model of the whole task design including practice trials containing novel sentences. Between each run subjects were reminded of the task instructions.

CHAPTER 4
RESULTS

Behavioral Results

Results of the behavioral analyses revealed significant differences between groups (Figure 4-1, Figure 4-2, Table 4-1, Table 4-2). Two repeated measures ANOVAs were conducted to compare the effect of task on 1) response latency (DV=RT), and 2) accuracy (DV=number of correct responses) in both the old and young groups. There was a significant effect of task on RT such that across groups, RT was significantly slower on task B than task A (F (1,28)=22.768, p <.001). Similarly, across groups, the number of correct responses was significantly less on task B than task A (F(1,28)=11.268, p <.01). In other words, across age groups, participants performed slower and produced fewer correct items during task B as compared to task A. Across tasks, there were also significant between groups effects of age on RT (F (1,28)=11.253, p <.01), and age on number of correct responses (F(1,28)=7.555, p <.01). In other words, the older group performed slower and produced more errors across tasks than the younger group.

Results also revealed a significant interaction between task and group for RT (F(1,28)=8.516, p <.01), meaning that the pattern of RT differences by task differed for each age group. Similarly there was a significant interaction between task and group for the number of correct responses (F(1,28)=13.991, p <.001), such that the differences between number of correct responses generated in each task varied by group.

In order to further clarify this interaction and to investigate our hypotheses regarding the effect of age and task on performance, group means were compared using t-tests. Overall, the Old group responded significantly slower than the Young

group across task conditions (t=-2.779, p<.05). Task comparisons examining only correct responses revealed no significant RT differences between groups on task A, though on task B, the Old group performed significantly slower than the Young group (t=-3.524, p<.01).

One question which we did not address directly was whether performance improved over time and if this varied by group. To investigate this somewhat indirectly, these RT differences were broken down and examined across runs in the scanner (Figure 4-3). For both groups, RT on task A did not differ significantly over time. Interestingly, on task B, RT for the young dropped after the first run, likely due to effective use of strategy, and remained constant for the remaining runs. In contrast, RT for the old group remained constant until the last run when RT suddenly decreased. These trends suggest that the young are benefitting much earlier than the old from effective use of strategy to complete task B and may provide evidence that the task is being performed differently by each group.

Results of the error analysis can be found in Table 4-2. A response was coded as an error in the initiation condition (task A) when a participant provided a response that did not complete the preceding sentence stem in an expected or sensible way. In the inhibition condition (task B) a response was defined as an error when it completed the sentence in a sensible way or had an obvious connection in meaning to the preceding sentence stem. These errors were further broken down into five error types as described in Table 3-2.

The Young group provided significantly more correct responses than the Old group on task B (t=3.496, p<.005), while group performance was not significantly

different on task A. The Old group missed or did not provide an answer to significantly more items on task B than the young group ($t(28)$=-2.752, p<.05), though again no significant group differences were discovered when comparing performance on task A.

The error analysis of incorrect responses to the inhibition task revealed that the Old group provided a significantly greater number of type C errors (i.e., correct completions of the sentence stem) than the Young group (t=-2.093, p<.05). No significant group differences were found for the semantically related error types (i.e., SO, SA, SB, SC).

FMRI Results

Effect of Task (Task vs. Rest)

Separate group analyses were completed to compare the mean activity during each task to the rest condition (Table 4-3). In both the young and old groups, increased blood oxygenation level dependent (BOLD) contrast in task A as compared to rest was associated with activity in frontal regions including Broca's area, inferior frontal gyrus, middle frontal gyrus and precentral gyrus, as well as middle temporal gyrus, and cuneus. Unique areas of activity in the young group relative to the old group included the anterior cingulate sulcus, the anterior cerebellum and the left dorsomedial and left lateral thalamus. Unique areas of activity in the old group included superior and inferior parietal cortices, superior temporal gyrus, pulvinar and putamen.

In task B when compared to the resting condition, both groups showed similar patterns of frontal and parietal activity to task A with the addition of DLPFC activity which was unique to task B for both groups. In the young group as compared to the old group during task B, activity was uniquely observed in precuneus, the left anterior nucleus and right dorsomedial nucleus of the thalamus and the left body of the caudate.

In the old group, unique activity compared to the young group consisted of superior and inferior parietal regions, angular gyrus, superior temporal gyrus, pulvinar and right putamen.

Across groups and tasks, activity in the cingulate gyrus and cingulate sulcus anterior to the corpus callosum showed negative activity (i.e. greater activity during rest than task), and this activity was greater in the young than the old groups. Prior studies (Hafkemeijer, van der Grond, & Rombouts, 2011; Koch et al., 2010) have indicated cingulate activity anterior to the corpus callosum are part of the default mode network (DMN) and that interruptions in the DMN occur with aging leading to decreased activation. Additional negative activity was found in subcortical regions for the old group including the anterior nuclei of the thalamus and right head of the caudate.

Unique Effects of Inhibition (Task B minus Task A) by Group

In the young group, the inhibition comparison was associated with greater activity bilaterally in dorsolateral prefrontal cortex (DLPFC), superior frontal gyrus (SFG), orbitofrontal cortex (OFC), precuneus, anterior cerebellum and the posterior cingulate gyrus, as well as activity in right angular gyrus and left supramarginal gyrus (Figure 4-5, Table 4-4, Appendix C). No areas showed greater activity for the initiation task than the inhibition task. In contrast, analysis of the old group did not reveal any areas associated with significant task differences in either direction. In other words no areas were found to be significantly more active in one task than the other for the old group.

Effect of Age (Old vs. Young) by Task

During Task A, the old group demonstrated greater activity than the young group in left precentral gyrus, left supramarginal gyrus, right angular gyrus and right parieto-occipital sulcus as well as bilateral activity in the paracentral lobule, inferior parietal

cortices, postcentral gyri and sulci, precuneus and cingulate cortex (Figure 4-6, Table 4-5, Appendix C). No areas were found to be associated with greater activity in the young than old group on task A.

Results differed for the inhibition condition. The old group showed greater activity than the young group in superior and medial frontal gyri, left precentral gyrus, bilaterally in superior and inferior parietal cortices, and posterior cingulate gyrus. The old group also showed greater negative activity in the right head of the caudate and prefrontal cortex than the young group (Figure 4-7, Table 4-6, Appendix C).

Effect of Age (Old vs. Young) on Inhibition (Voxel by Voxel B-A)

To further describe the results of the group and task differences, the AUC during task A was subtracted from the AUC during task B for each voxel of each participant. Using these voxel by voxel models of inhibitory activity, an independent samples t-test between old and young groups revealed consistently greater activity in the young than the old in the left cuneus (BA 7), cingulate (BA 23 and 32), left superior parietal lobe (BA 5/7), right orbitofrontal cortex (BA 47/11), and right DLPFC (BA 9) (Figures 4-8, 4-9; Table 4-6).

Correlational Analysis (Brain vs. Behavior)

To clarify the relationship between brain activity differences in older adults and behavioral performance on the task, average RT for each participant in the old group during task B was correlated with brain activity as measured by average AUC in the clusters generated by the old vs. young comparison. Although originally planned, correlations were not completed using the number of correct responses due to the fact that the data were non-normally distributed with an average number of correct responses of 26.6 out of 30 or 88% correct. For the old group, significant positive

correlations were found between increased RT during task B and increased bilateral midline activity in the medial and superior frontal gyri (MFG/SFG), (r_s=.518, p<.05); the left superior parietal lobe/post central gyrus (r_s=.668, p<.01) and right head of the caudate (r_s=.59, p<.05; Figure 4-4). Although it may seem counterintuitive since the activity in the caudate was negative, the correlation with RT revealed that greater negative activity is associated with faster responding.

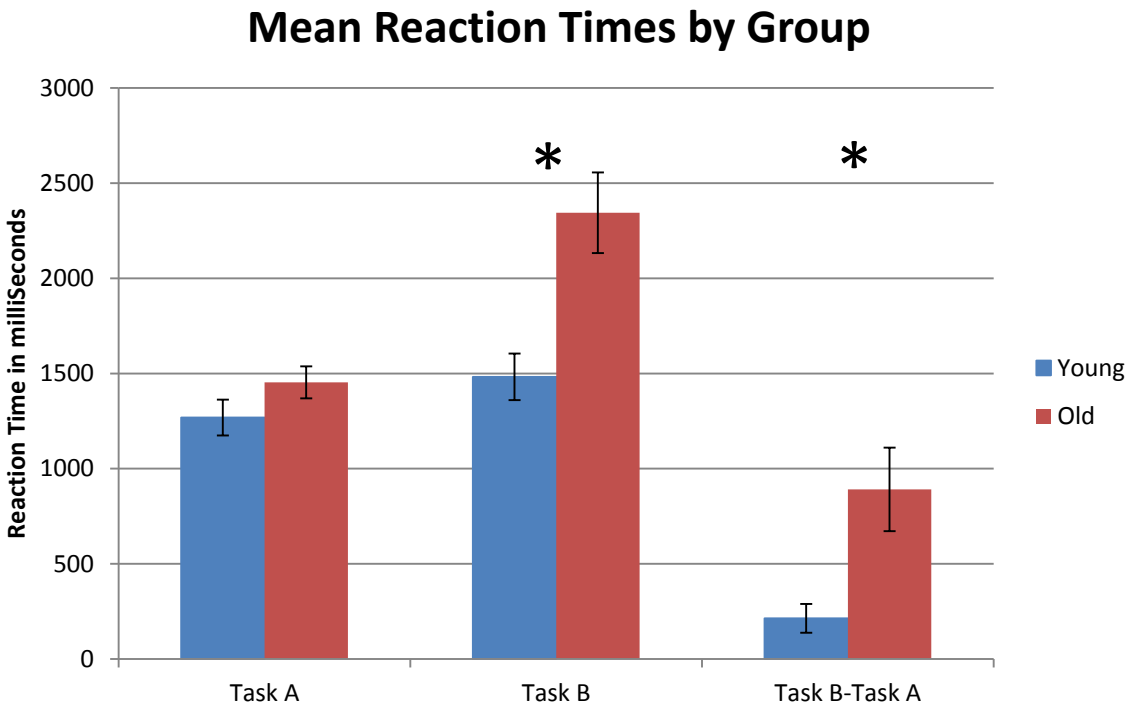


Figure 4-1. Mean reaction times by group and task. * Indicates significant group difference (p<.05); RT = reaction time.

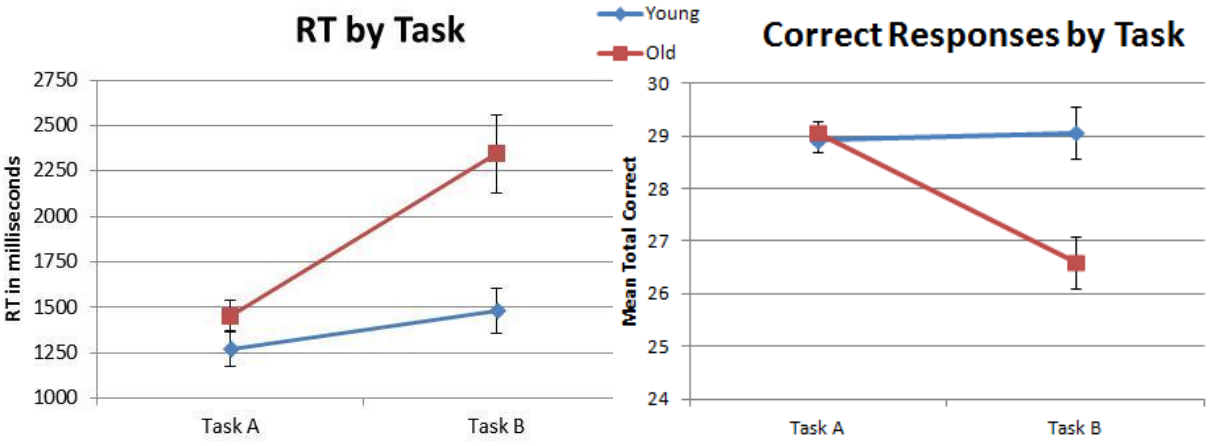


Figure 4-2. Mean behavioral performance by group and task.

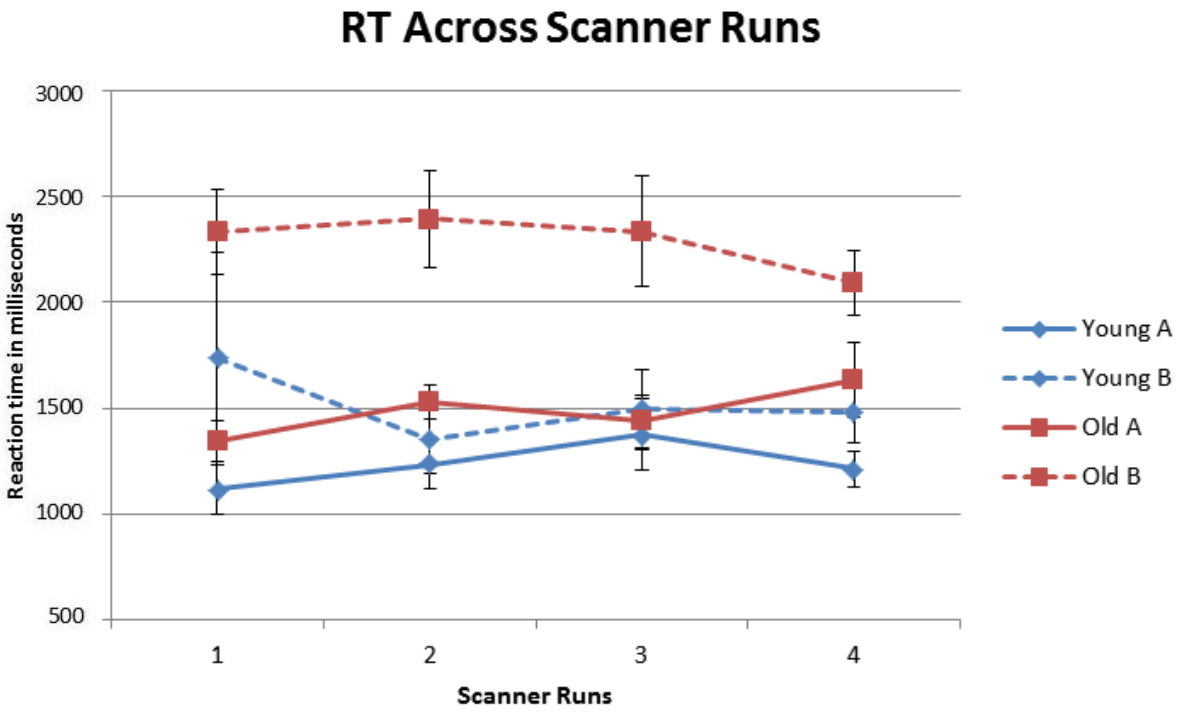


Figure 4-3. Average RT by group plotted across time with standard error bars representing variability. For both groups, RT on task A did not differ significantly over time. On task B, RT for the young dropped after the first run, likely due to effective use of strategy, and remained constant for the remaining runs. RT for the old group, remained constant until the last run when RT suddenly decreased. These trends suggest that the young are benefitting much earlier than the old from effective use of strategy to complete task B and may provide evidence that the task is being performed differently by each group.

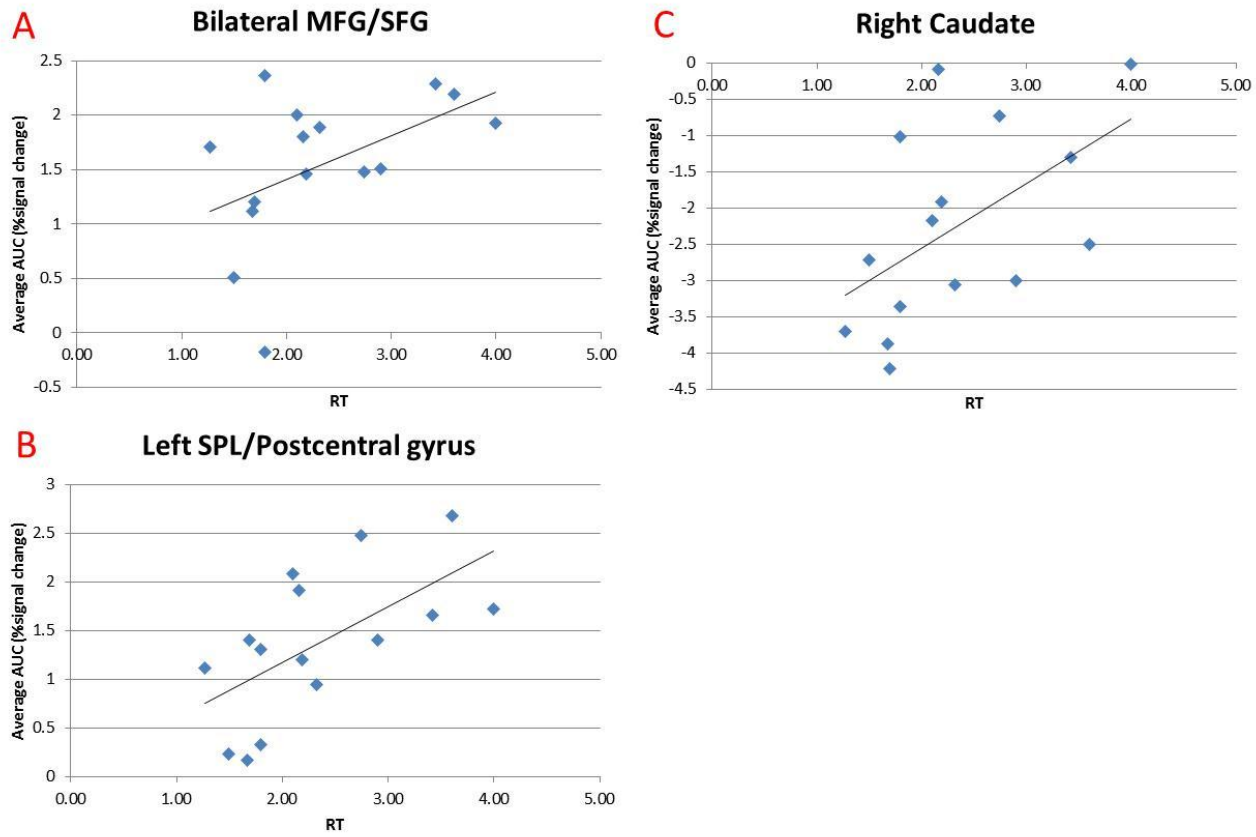


Figure 4-4. Correlations between average AUC activity for older participants during task B and RT for correct responses in task B. Spearman's rank coefficients were as follows A: r_s=.518, p<.05; B:r_s=.668, p<.01; C:r_s=.59, p<.05.

Table 4-1. Average group behavioral performance by task.

	Group	A RT	*B RT	A Correct	*B Correct	A NR	B NR
Mean(SD)	Young	1268(363)	1482(473)	28.93(0.88)	29.07(0.96)	0.13(0.35)	0.40(0.91)
	Old	1453(325)	2344(820)	29.07(0.88)	26.60(2.56)	0.40(0.63)	2.13(2.26)

Notes: * = Significant difference between group means p<.05; A RT = reaction time on task A in ms; B RT = RT on task B in ms; Correct=total correct responses out of 30 possible items; NR= number of unanswered items; SD = standard deviation.

Table 4-2. Error analysis of task B responses based on Burgess & Shallice's rater classification guide (1996).

	Group	C Error*	SO Error	SA Error	SB Error	SC Error
Mean (SD)	Young	0.53(0.64)	0.13(0.52)	0.87(0.92)	0.87(1.51)	1.20(1.15)
	Old	1.27(1.33)	0.33(1.05)	0.93(1.62)	0.80(1.26)	1.13(1.13)

Notes: * = Significant difference between group means p<.05; C Error = the word reasonably completes the sentence; SO Error = the word is an opposite of what you might expect; SA Error = the word is semantically connected to the subject of the sentence; SB Error = the word is semantically connected to the expected response; SC Error = word vaguely fits in a way that makes the sentence ludicrous.

Table 4-3. Effect of Task: Cluster locations by group based on one sample t-tests

Cluster Location		Young A	Young B	Old A	Old B
Cortical	Frontal	Broca	Broca	Broca	Broca
		IFG	IFG	IFG	IFG
		MFG	MFG	MFG	MFG
		PreCG	PreCG	PreCG	PreCG
			DLPFC		DLPFC
	Parietal		preCuneus	˜SPL	˜SPL
				˜IPL	˜IPL
		SMG		SMG	SMG
					˜AG
	Temporal			˜STG	˜STG
		MTG	MTG	MTG	MTG
	Occipital	Cuneus	Cuneus	Cuneus	Cuneus
	Cerebellum	Ant.lobe	Ant.lobe		
	Cingulate	*AC_S	*AC_S	*AC_G	*AC_G
		*AC_G	*AC_G		
Subcortical	Thalamus	L-DMN	L-AN	˜Pulvinar	*AN/VA
		L-LN	DMN		˜DMN
	Striatum		L-$Caudate_B$	˜Putamen	˜*R-$Caudate_H$
					˜R-Putamen

Notes: Clusters size ≥ 215 voxels, thresholded at an uncorrected p-value of .001 to achieve a family-wise error corrected alpha level of .05. Activity is bilateral unless specified; R=right, L=left; Broca=Broca's area (pars opercularis, pars triangularis);IFG=Inferior Frontal Gyrus; MFG=Medial Frontal Gyrus; DLPFC=dorsolateral prefrontal cortex; PreCG=PreCentral Gyrus; AC_S=Anterior Cingulate Sulcus; AC_G=Anterior Cingulate Gyrus; SPL=Superior Parietal Lobe, IPL=Inferior Parietal Lobe; SMG=Supramarginal Gyrus; AG=Angular Gyrus; STG=Superior Temporal Gyrus; MTG=Medial Temporal Gyrus; AN=Anterior nucleus of the thalamus; VA=Ventral anterior nucleus of the thalamus DMN=Dorsomedial nucleus of the Thalamus; LN=Lateral nuclei of the Thalmus; $Caudate_H$=Head of Caudate; $Caudate_B$=Body of Caudate;* = negative BOLD; ˜=unique area in Old

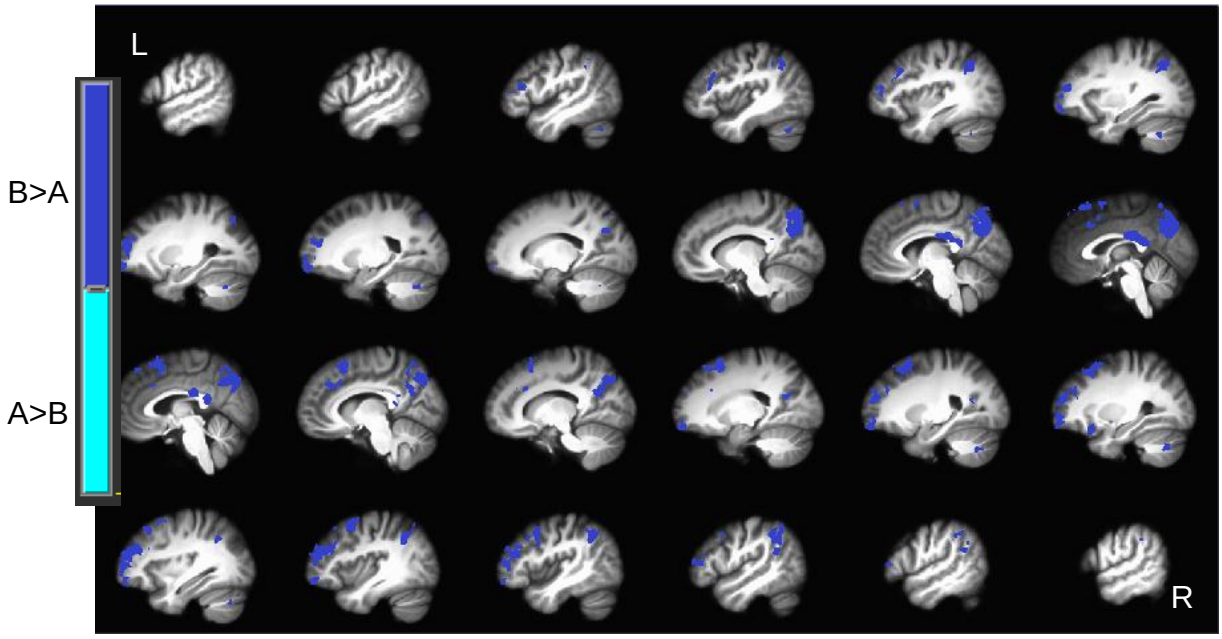


Figure 4-5. Effect of Inhibition (task B-task A) for young group based on paired sample t-tests. P<.0001. All areas are greater AUC for task B than A. Table 4-4 contains descriptions of clusters.

Table 4-4. Effect of Inhibition (task B-task A): Cluster locations for Young group based on paired sample t-tests

Cluster Location		BA	#Voxels	X	Y	Z
Frontal	R-DLPFC	46,11,10,9 8	22642	-27.6	-34.4	30.3
	L-DLPFC	46	1584	41.3	-29.4	21.8
	R-SFG	8/9	330	-3.3	-40.9	51.4
	R-OFC	25	601	-28.4	-21.1	-18.2
	L-OFC	10	2694	27.9	-50.1	13.7
	L-OFC	11	1909	24.2	-59.5	-9.7
Parietal	Precuneus	7	15322	0.2	68.4	38.3
	R-Angular	39	4163	-46	50.8	38.9
	L-SMG	40	2696	34.7	58.4	40.9
Cerebellar	L-Ant. lobe		985	31	61.9	-36
	R-Ant.lobe		667	-28.1	66.5	-38.9
Cingulate	PostCinG	23	4026	0.6	33	21.4

Notes: Clusters included contained at least 215 voxels and were thresholded at an uncorrected p-value of .001 to achieve a family-wise error corrected alpha level of .05. BA=Brodmann Area; DLPFC=dorsolateral prefrontal cortex; SFG=Superior frontal gyrus; OFC= Orbitofrontal cortex; SMG=Supramarginal Gyrus; Ant. Lobe=anterior lobe; PostCinG=Posterior Cingulate gyrus

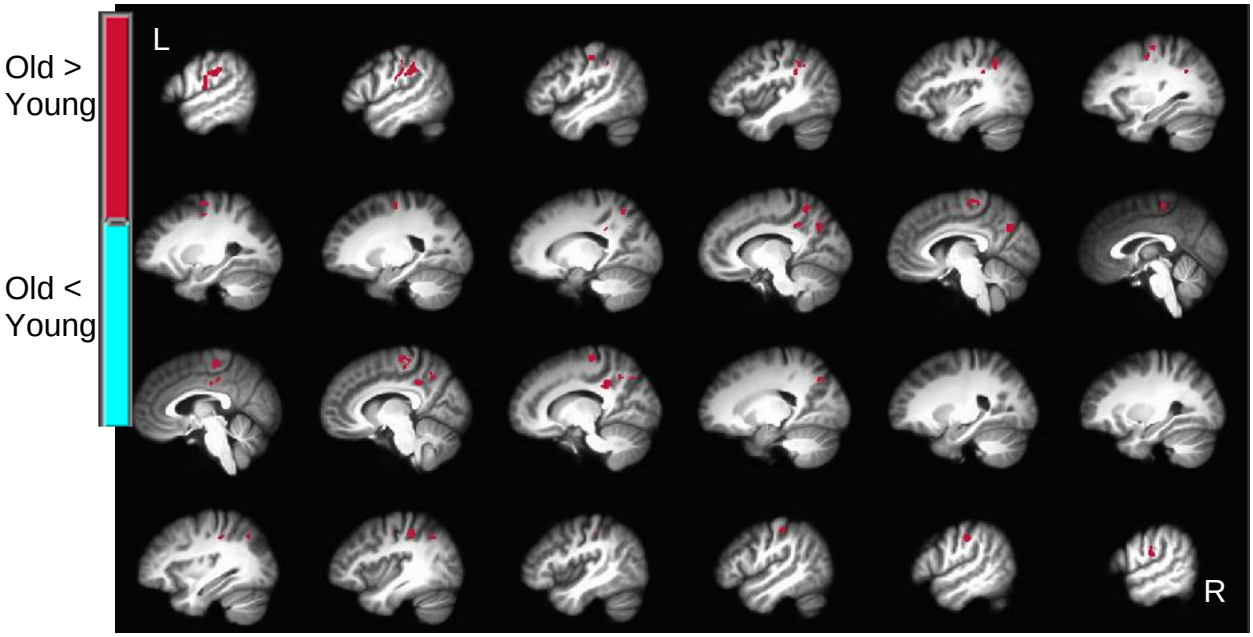


Figure 4-6. Effect of age (Old-Young) on task A based on independent sample t-tests. p<.00009. Table 4-5 contains descriptions of clusters.

Table 4-5. Effect of Age (Old-Young) during Task A: Cluster locations by task based on independent samples t-tests

Cluster Location		BA	# Voxels	x	y	z
Old>Young						
Frontal	L-Superior PreCG	4	540	26.2	14.4	59.7
		4	246	29.4	11.2	48
	Paracentral lobule	5/3,1,2	1688	-4.8	26	61.2
Parietal	L-IPL	43/40	1957	53.9	23.5	27.3
	R-IPL	43/40	338	-59.2	14.9	22.8
	L-SMG	40	1056	38.1	47.4	36.1
	R-PostCS		929	-45.5	27	43.4
	L-PostCG (superior)	3,1,2	249	47.8	23.6	45.3
	R-Angular gyrus	39	239	-36.7	59.3	40.3
	R-Precuneus	7	309	-10.6	57	43.1
	L-Precuneus	7	716	9	68.6	32.9
		7	485	11.7	54.6	54.4
Cingulate	R-CinG	23	227	-5.4	23.6	37.8
		31	781	-13	41	34.7
	L-PostCinG	31	336	12.2	42.1	34.9
Occipital	R-Parieto-occipital sulcus		262	-17.3	71.1	40.9

Notes: Clusters included contained at least 215 voxels and were thresholded at an uncorrected p-value of .00009 to achieve a family-wise error corrected alpha level of .01. PreCG=precentral gyrus; IPL=inferior parietal lobe, SMG=supramarginal gyrus; postCS=postcentral sulcus; postCG=postcentral gyrus; CinG=cingulated gyrus; PostCinG=posterior cingulate gyrus

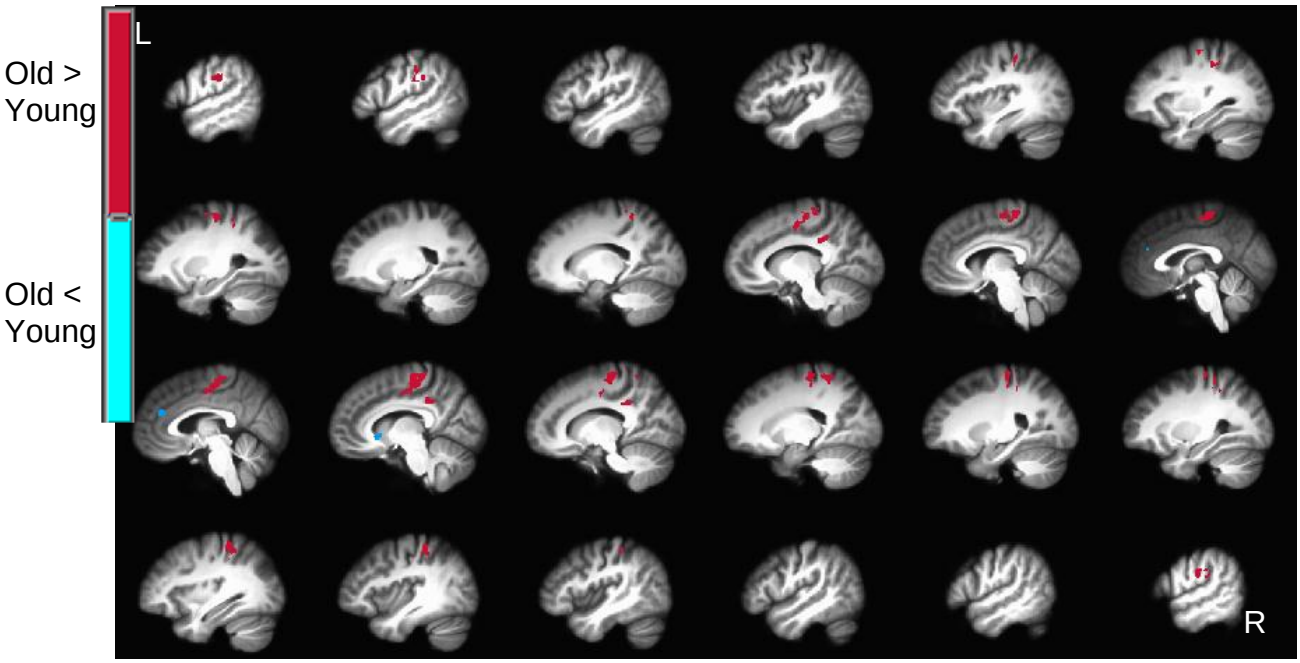


Figure 4-7. Effect of age (Old-Young) on task B based on independent sample t-tests. p<.00009. Table 4-6 contains descriptions of clusters.

Table 4-6. Effect of Age (Old-Young) during Task B: Cluster locations by task based on independent samples t-tests

Cluster Location		BA	# Voxels	x	y	z
Old>Young						
Frontal	MFG, SFG	4/5/3,1,2	6426	-5.4	22.6	57.6
	L-Superior PreCG	4	607	27.2	18.0	58.5
Parietal	R-postCG	3,1,2	1552	-34.7	35.5	53.0
	L-postCS/IPL	3,1,2/40	1038	53.1	25.1	32.2
	R-postCS/IPL	3,1,2/40	818	-6.1	20.2	25.1
	L-Superior postCG	3,1,2	566	31.7	34.5	47.2
	R-SPL/postCG	3,1,2	563	-18.4	43.9	61.2
	L-SPL/postCG	3,1,2	232	17.8	41.3	60.3
Cingulate	R-PostCinG	23	689	-11.2	38.7	34.4
	L-PostCinG	23	365	11.2	37.4	32.3
Young > Old						
	R-Caudate$_H$		221	-8.2	-17.8	-4.1
	Medial PFC/ CinS	32	351	-2.4	-39.6	21.8

Notes: Clusters included contained at least 215 voxels and were thresholded at an uncorrected p-value of .00009 to achieve a family-wise error corrected alpha level of .01. SFG=Superior frontal gyrus; OFC= Orbitofrontal cortex; MFG=Medial Frontal Gyrus; PreCG=Pre Central Gyrus; PostCG=Post Central Gyrus, postCS=Post Central Sulcus; CinS=Cingulate Sulcus; PostCinG=Posterior Cingulate Gyrus; IPL=inferior parietal lobe; PFC=prefrontal cortex

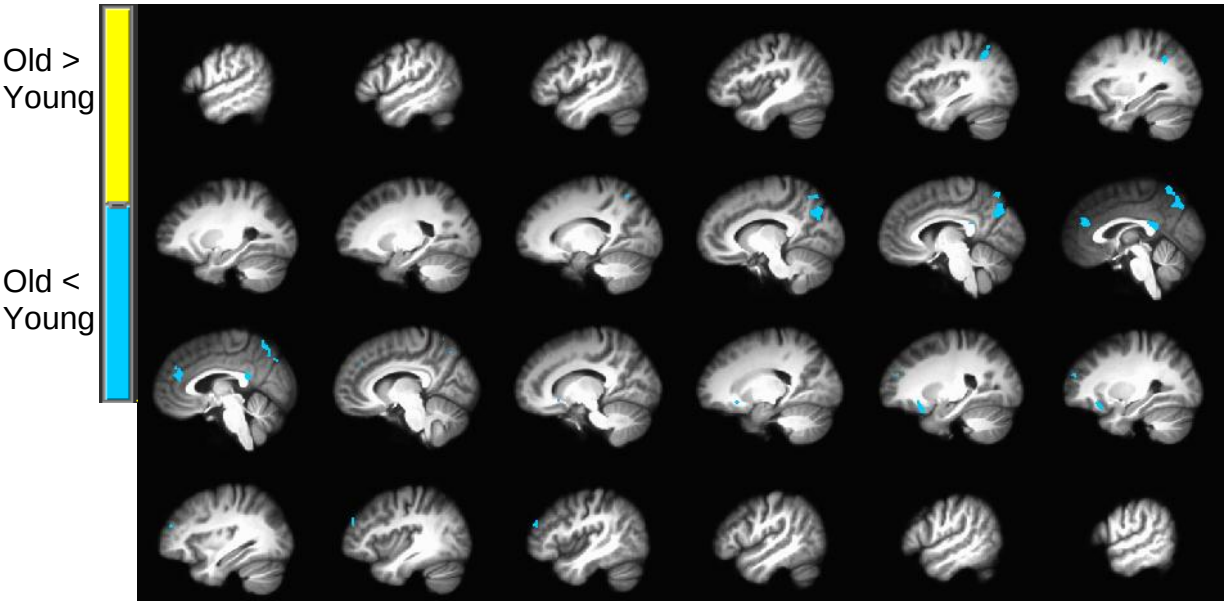


Figure 4-8. Effect of inhibition (B-A) compared between groups based on independent sample t-tests. p<.0001. Clusters represent areas of significant age related activity differences associated with inhibition. Figure 4-8 and Table 4-7 contain descriptions of clusters.

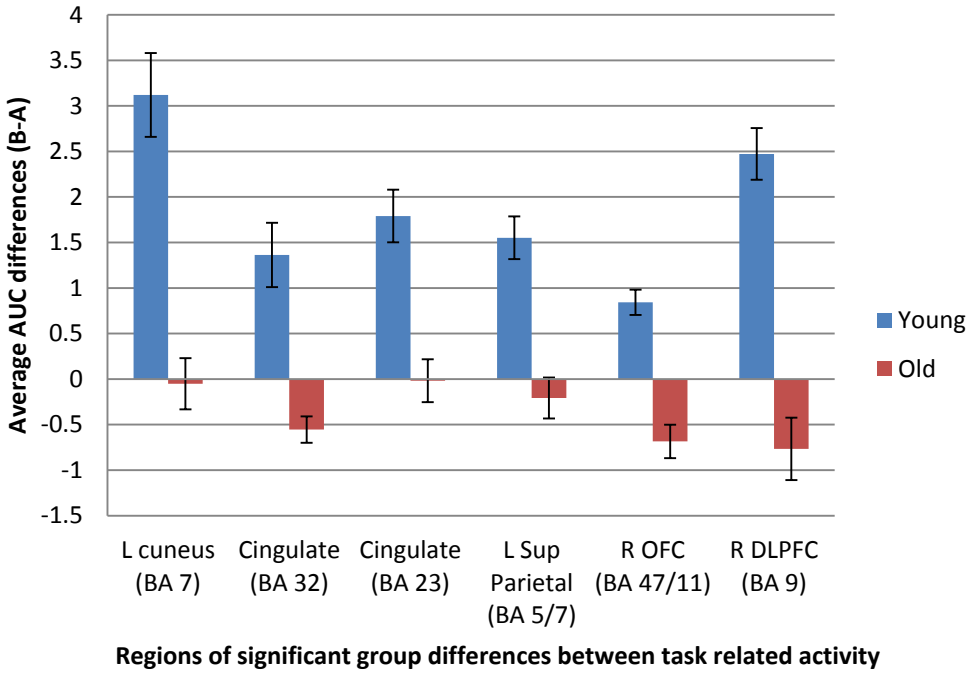


Figure 4-9. Age differences in activity associated with inhibition. Average AUC differences (B-A) in clusters found to be significantly different between old and young groups. L=left; R=right; Sup=superior; OFC=orbitofrontal cortex; DLPFC=dorsolateral prefrontal cortex.

Table 4-7. Age differences in activity associated with inhibition based on independent samples t-tests.

Cluster Location	BA	# Voxels	x	y	z
Young>Old					
Left Cuneus	7	3633	3.2	67.9	50.0
Cingulate (bilateral act.)	32	1290	-1.9	-40.6	23.2
Cingulate (bilateral act.)	23	846	0.4	41.1	19.0
Left Superior Parietal	5/7	812	34.4	56.3	41.3
Right Orbitofrontal	47/11	727	-24.7	-21.8	-16.4
Right DLPFC	9	615	-38.7	-49.2	24.8

CHAPTER 5
DISCUSSION

This study explored the neural correlates of inhibitory processes in language and how they differ in older and younger adults. Using a modified version of the Hayling test (Burgess & Shallice, 1997) during fMRI we were able to examine the neural correlates of differences in task performance between healthy older adults and healthy younger adults and compare related brain activity to behavioral performance. While sentence completion tasks have been used in a handful of imaging studies in order to examine aspects of inhibitory processes (Allen et al., 2008; Collette et al., 2001; Nathaniel-James et al., 1997), none have examined the effects of age on inhibitory neural correlates.

Effects of Age on Inhibition

In order to explore this complex question, a few levels of analyses were completed. To facilitate interpretation of these results, we will explore the most complex analysis first and then attempt to understand it using results from the other analyses.

The primary purpose of this study was to examine age related changes in the neural correlates of inhibition. Thus, we examined a voxel by voxel comparison of task related activity differences (i.e., activity during task A subtracted from activity during task B) for each participant to model inhibition in each voxel. Then, we compared the resulting activity differences across groups (Figure 4-8, Table, 4-7). Significant clusters in this analysis, therefore, represent regions in which there were group (old vs. young) differences in activity required to support inhibition in task B over activity required to support task A.

Regions found to have greater task differences between groups (e.g., left cuneus (BA 7), cingulate cortex (BA 23 and 32), left superior parietal lobe (BA 5/7), right orbitofrontal cortex (BA 47/11), and right DLPFC (BA 9)) all revealed greater activity differences in the young group than the old group (Figure 4-9). These results were unexpected given that the older adults performed task B significantly slower than the young adults and showed greater RT differences between tasks (Figure 4-1) which we had hypothesized would lead to increased activity differences.

In order to comprehend these seemingly conflicting results we must turn to our earlier analyses. Most importantly, the results examining the effect of inhibition within each group (Figure 4-5, Table 4-4, Appendix C) informed us that though significant regions of activity (bilateral DLPFC, SFG, OFC, precuneus, anterior cerebellum, posterior cingulate gyrus, right angular gyrus and left supramarginal gyrus) were associated with inhibition in the young group, no such differences were found in the old group. Lack of significant task differences in the old group suggests that similar networks were being utilized to perform both task A and task B, but this comparison does not tell us what areas the old group used to perform tasks A and B.

Again, we can turn to an earlier analysis for clarification. The comparison of activity associated with the effect of task (i.e., task vs. baseline) confirms that there was in fact significant task related activity (Appendix C, Table 4-3) for the old group during both tasks A and B and that the regions of activity were remarkably similar. It appears that those regions recruited by the young group during task B were already in use during task A for the old adults and therefore could not be differentially engaged in task B.

This explanation clarifies why we did not find areas of greater task related differences in the old group in our overall analysis of the effect of age on inhibition, but it does not completely explain how the behavioral results relate to functional imaging results. A review of the analysis exploring the effect of age (i.e., old vs. young) found that during both tasks, regions of group differences predominantly demonstrated greater activity in the old than the young group (Figure 4-6, Figure 4-7, Table 4-5, Table 4-6). There are two possible explanations for greater activity in old than young adults: (1) Old adults may need an activity increase to support performance of tasks that have become more difficult with age. (2) There may be a loss of the ability of one brain area to suppress other brain areas during task performance, resulting in less differentiated activity in the old than the young group. Under the latter hypothesis, additional areas of activation could cause interference and decrease the efficiency of performance. For the current data, brain regions engaged during both tasks were similar in spite of behavioral results indicating that task B was more challenging for old adults; i.e., old adults performed task B more slowly and produced more errors than young adults. The theory of compensation is insufficient to explain this age-related activity difference. If it had been compensatory, old adults would have shown greater activity during task B than A in order to compensate for the difference in task difficulty. Instead, these data tend to support the loss of inhibition theory because of the greater activity for old adults than young adults in task A, which was less difficult than task B and behaviorally showed similar reaction times and accuracy between the groups (Figure 4-2).

However, this is not the whole story. While most clusters during task B showed greater activity in old than young adults, two exceptions were found: The right head of

the caudate nucleus and the medial PFC/ anterior cingulate sulcus both demonstrated greater activity in the young than the old group. These data generate two additional questions. First, what is the meaning of the two regions for which the young adults demonstrated greater activity during task B than the old adults? Second, are any of these regions associated with group behavioral performance differences on task B (i.e., RT)? To begin, we can review the hemodynamic response functions (Appendix C) for these two regions. In most of the clusters of activity, the pattern of activity is similar in both groups though the activity is greater in old than young adults. In contrast, in both of these regions what we find is positive activity in the young and negative activity in the old. In other words, one cannot simply state that the young are showing greater task B related activity in those areas; it also must be noted that the old adults are demonstrating suppression of activity. This is unique for old adults relative to previous studies in our laboratory. Specifically, McGregor et al. (2011) showed a loss of suppression of motor cortex ipsilateral to unilateral hand movement in old adults, and Meinzer et al. (in press) and Zlatar (unpublished) showed a loss of suppression of default mode network activity in old adults during word generation. Thus, it is not true that old adults always lose the ability to suppress brain activity during an active task. This phenomenon may be specific to the task at hand rather than a general characteristic of the older brain.

To complicate things even more, our correlation analyses (Figure 4-4) found significant positive correlations between the activity in the right head of the caudate and response latency during task B for the older adults. In other words the more negative the activity in the right head of the caudate, the faster the participant performed task B.

This finding indicates that suppression of right caudate head activity may be important for optimal task performance for old adults. Why suppressed caudate performance would be helpful in task B performance for old adults is unclear. The medial frontal cortex, which also showed increased activity in young adults and decreased activity in old adults, did not demonstrate any correlation between task-related activity and behavior.

One final finding is worth discussing. For some of the areas showing activity differences between groups, the associated time courses (Appendix C) include only the declining portion of the hemodynamic response function, suggesting that the activity is related to an event starting prior to the time period we modeled, i.e., giving the word at the end of the sentence. This activity is most likely associated with the reading that occurred before the response we modeled. Although we attempted to control for reading speed by presenting the words of the sentence stems one at a time, other aspects of reading may have introduced additional variability. We designed the study so that the words of the sentence stem remained on the screen during the response period in order to remove potential task difficulty due to working memory issues. However, this may also have encouraged old participants to reread the words in the sentence stem while simultaneously anticipating the response to be given at the end of the sentence.

Strengths and Weaknesses

A general difficulty with this study and the goal of investigating the neural correlates of inhibitory processes is that the concept of inhibition itself is somewhat vague. In a motor paradigm, it is much easier to define the initiation and inhibition of a given task and to determine when the inhibition likely begins and ends. In the extended cognitive paradigm used in this study (i.e., sentence reading and completion), the

inhibitory event may be less discrete and probably involves a few simultaneous or sequential processes. For example, in task B our analyses were performed on the fMRI images which occurred immediately after the cue to respond at the end of the sentence stem. Participants were instructed not to respond prior to that cue and our assumption was that after reading all the words of the sentence stem, a participant would engage the semantic network needed for a correct response, inhibit that response and retrieve a new unrelated response before initiating a verbal response. By presenting the words of the sentence stems one at a time, we hoped to prevent the inhibition from beginning until just after the last word of the sentence stem was read. However, in reality, reading each word of the sentence stem may bring a participant one step closer to knowing how the sentence will end and it is entirely possible that the inhibitory semantic processes are co-occurring while the participant is reading the sentence. This may explain why it was difficult to find evidence of typical HDR functions in the time period for which we analyzed these data. The argument can be made that a comparison of fMRI activity during task A to that of task B should eliminate the confounds of reading and the general processing which leads up to generating a word which completes the sentence; however, it seems clear from our data that it is not that simple. Semantic inhibition may be better thought of as a process which occurs over time, in stages, as information is gathered that can help inform the selection of a desired response or cognition. This way of thinking about inhibition means that for future studies extreme care should be taken to design an extremely simple yet elegant task which allows for a time-limited characterization of inhibitory processes.

In addition, it is unclear if old and young participants may have differentially benefitted from the use of strategies to complete the inhibition task and thereby introduced a confound into the inhibitory process we were trying to examine (Figure 4-3). In order to further investigate aging related changes to the neural correlates of semantic inhibition, it will be important to control for strategy use possibly by increasing the task difficulty, providing a strategy, or designing a task which does not allow for consistent use of strategies.

In summary, as improvements in health care increase longevity, thereby facilitating growth of the aging population, the scientific community is increasingly motivated to study the cognitive changes which accompany biological aging. The literature is currently inundated with aging research. Although huge strides have been made in our understanding of the neural correlates of cognitive changes associated with pathological aging for a variety of disorders, our understanding of normal, non-pathological aging is still lagging behind. As normal aging is a process that none of us can escape, and heavily impacts other pathological processes, it is essential that we continue attempting to understand the aging brain as the baseline state from which pathological aging departs. It is well known that consistent differences exist between older and younger adult brains, though the reasons for these differences and what they mean for behavioral performance and development across the lifespan is an area of study that needs considerably more investigation. Specifically, in the area of language studies, we have assumed for a long time that the younger brain is an adequate model for diseases of aging (stroke, Alzheimer's disease, Parkinson's disease, etc.). For example, we have failed to take into account increases in right-hemisphere and other activity during

language tasks for older adults when we interpret findings in studies of aphasia. Previous findings (Meinzer et al., in press; Wierenga et al., 2008) indicate that we can no longer ignore the effects of aging on brain-language functions. Findings from the current study have extended these previous findings and also suggest that we are still unraveling the complexities of age-related changes in the brain's language systems.

APPENDIX A
SENTENCE STEMS INCLUDED IN TASK

A	B
1. Jeff was sent to bed without	31. The thick mud stuck to her
2. He had to fill his truck with	32. Barry wisely chose to pay the
3. Scotty licked the bottom of the	33. Surgery was needed to repair his failing
4. Every month Rick had to clean his	34. He was miles off the main
5. The girl was advanced for her	35. Our new green car blocked the narrow
6. Dan caught the ball with his	36. The earth is shaped like a
7. Diane slowly sank into the hot	37. Helen reached up to dust the
8. Suzy liked to play with her toy	38. Matt was wild when he was
9. Did you want to go to the	39. He smiled and sat down at the
10. He wondered if the storm would be	40. My aunt likes to read the daily
11. They were startled by the sudden	41. They took short trips during the
12. My uncle gave my mother a big	42. He put his feet up on the
13. Plants will not grow in dry	43. Jim had learned the special passage by
14. Some of the ashes dropped on the	44. Jack hit his horse with a
15. Her dress was made of very fine	45. Bob thought she had a friendly
16. The wooded lake made a pretty	46. Larry chose not to join the
17. In the morning Jake took out the	47. The apple pie had a delicious
18. The cup of tea felt very	48. What you find depends on where you
19. Tim would often sleep during his lunch	49. Paul has always wanted to be a
20. The final score of the game was	50. In the park the hippie touched the
21. No one wanted to accuse him of	51. She cleaned the dirt from her
22. Most students prefer to work during the	52. He drove the nail into the
23. Don found that he had no spare	53. The little girl was afraid of the
24. She locked the valuables in the	54. My father and mother are getting
25. You can't buy anything for a	55. Harriet sang while my brother played the
26. John poured himself a glass of	56. Stan slowed down going around the
27. After speaking Allen left the noisy	57. Few nations are now ruled by a
28. Even their friends were left in the	58. Jill looked back through the open
29. The choir sang hymns while the people	59. Before jogging, it's a good idea to
30. Joan showed her friend a new card	60. Not even the cast liked the

APPENDIX B
INSTRUCTIONS FOR SENTENCE COMPLETION TASK

Outside Scanner Instructions

Practice trials

"There will be two types of sentence completion tasks you will be doing today. I'll explain each one to you and let you have a chance to practice before you go in the scanner."

Bring up practice items:

"In a moment you will see a series of sentences each of which has the last word missing from it. For the first task I want you to carefully read each sentence and when the blank appears, your job is to give me a word which completes the sentence. Do you understand?
Are you ready?"

Run through two examples.

"The next few sentences aren't really any more difficult than the ones you've just done. But the important thing is that I want you to give me your answer as quickly as you can, the faster the better. Ok?"

Run through the rest of practice for part A.

"Now we are going to move on to the second task. Again, you will see a series of sentences with the last word missing just like the ones you have already done, but this time I want you to give me a word which does not fit at the end of the sentence, I want the word you give me to be completely unconnected to the sentence in every way. Do you understand?
Are you ready?"

Run through two examples.

"Ok now let's do some more practice items. Remember that the words you give me must be unconnected to the sentence and that it is important for you to give me your answer as quickly as you can. Are you ready?"

Run through the rest of practice for part B.

Issues to correct if they come up during practice trials:

1. *If a subject gives an answer consisting of three words or more, say:*

"You've just given me an answer which was more than one word. This doesn't matter too much, but I would prefer it if you would try to keep your answers to just one word."

2. *The first time a subject gives a related word for the second part say:*

"The word you have just given me DOES fit at the end of the sentence. The sentence [*read sentence with completed word*] does make sense, doesn't it? But what I want is a word which DOESN'T fit at the end; one which is completely unconnected to it. So for instance if you have given me the word "banana" that would be right, because "banana" is unconnected to the sentence [*read sentence*]. So can you think of a word which you could have given me instead of [***subject's response***]?"

Let the subject try again, then move on to the next practice item, regardless of whether they produce an unconnected word. If the response is acceptable, just say:

"That's very good, so let's try another one."

If the response is not acceptable (i.e. strongly connected to the sentence), say:

"Well that word is still connected to the sentence so it's not an ideal kind of answer, but let's try another to see if you can get the hang of it."

3. *Any other time the subject gives a related response for second part say:*

"You have given me a word which completes the sentence and remember, what I want is a word which DOESN'T fit at the end; one which is completely unconnected to it."

4. *If subject repeats responses say:*

"You have already used that answer. Repeating the same word to each sentence is a good way of approaching this test, but it makes it too easy, so I'm afraid that I'm going to have to ask you not to use it. From now on I want a different word each time."

5. *If a subject asks about other strategies, say:*

"The only strategy not allowed is repeating answers."

(BUT do not under any circumstances give examples of other strategies they might use).

After the practice items:

"In the scanner you will be seeing more sentences just like the ones you practiced. There will blocks of sentences where your task will be to complete the sentence, and other blocks where your task will be to give unconnected words.

Before each group of sentences, a screen will pop up showing the word 'Complete' or 'Unconnected'. If the word 'Complete' comes up, make sure you give a word that completes the sentence, if the word 'Unconnected' comes up make sure the word you give is unconnected to the sentence in every way. Do you understand? Any questions?"

Inside Scanner Instructions

Just before the scanner task:

"We're now ready to start the sentence completion task. For each group of sentences, remember that your job is to read the sentences carefully and say a word based on the instruction screen. If the word 'GOOD' comes up, make sure you give words that complete the sentences, if the word 'UNRELATED' comes up make sure the words you give are unconnected to the sentences in every way. It is also important for you to give me your answer as quickly as you can the faster the better. Ok?"

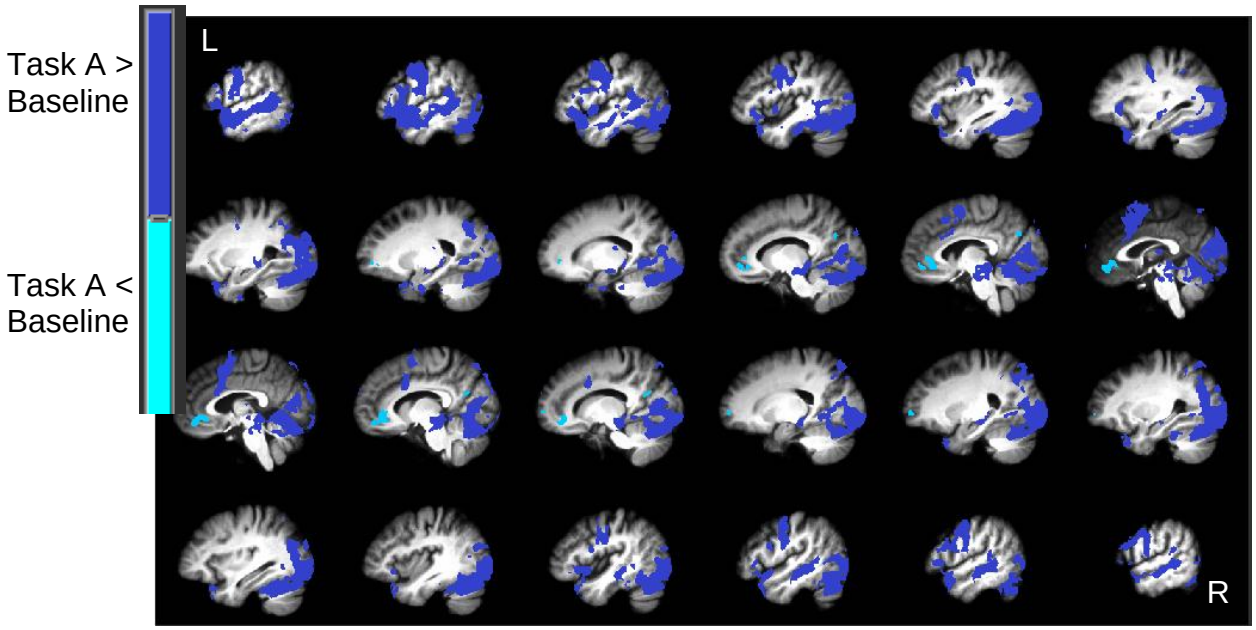
Before a new run:

"We're ready to start the next run.
Remember, if the word 'GOOD' comes up, make sure you give words that complete the sentences, if the word 'UNRELATED' comes up make sure the words you give are unconnected to the sentences in every way. And please give your answers as quickly as possible!"

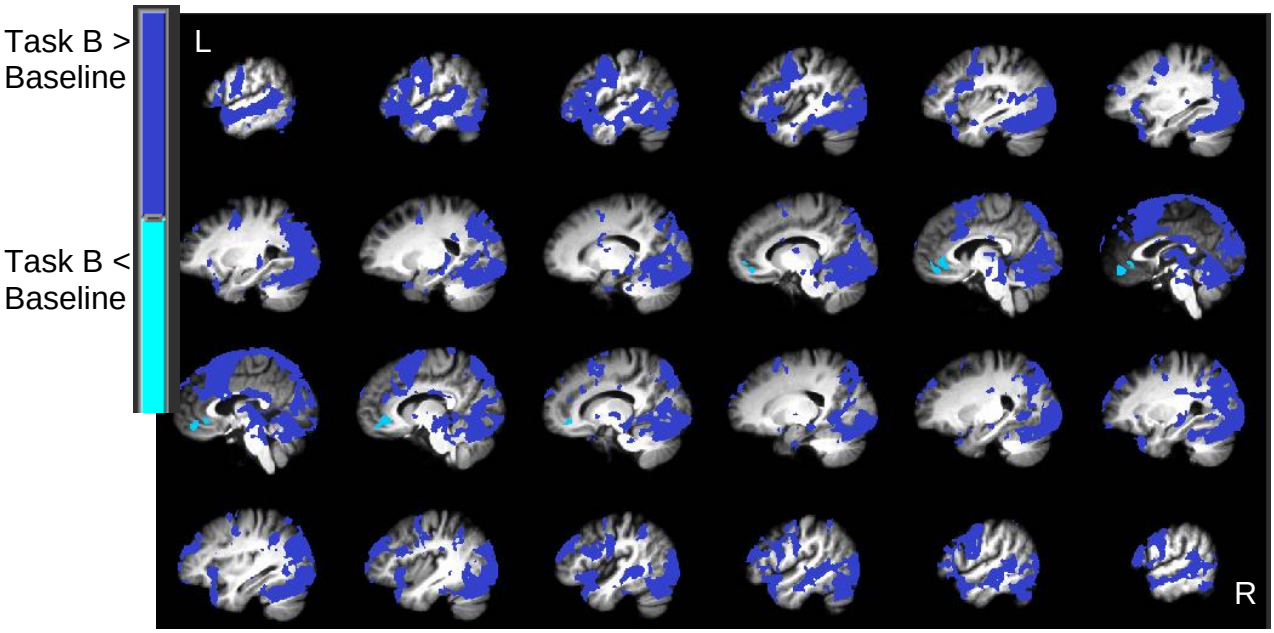
APPENDIX C
MONTAGES OF FMRI CLUSTER ACTIVITY WITH ASSOCIATED AVERAGE HEMODYNAMIC RESPONSE FUNCTIONS

Effect of Task (Task vs. Baseline)

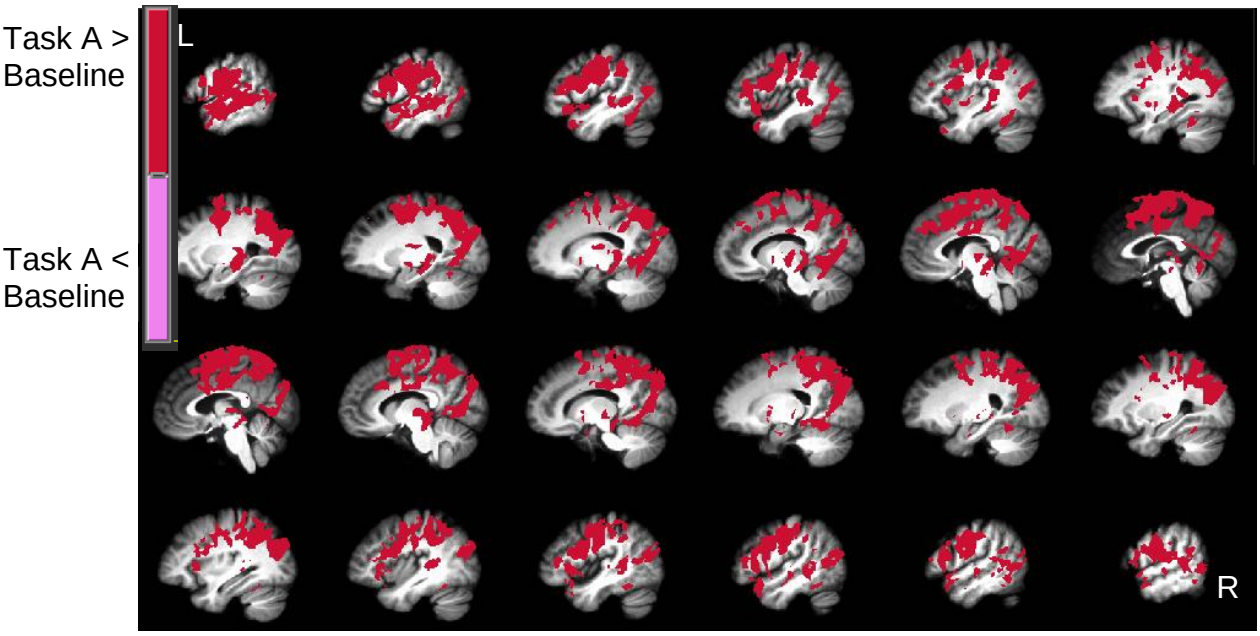
Young: Task A vs. Baseline



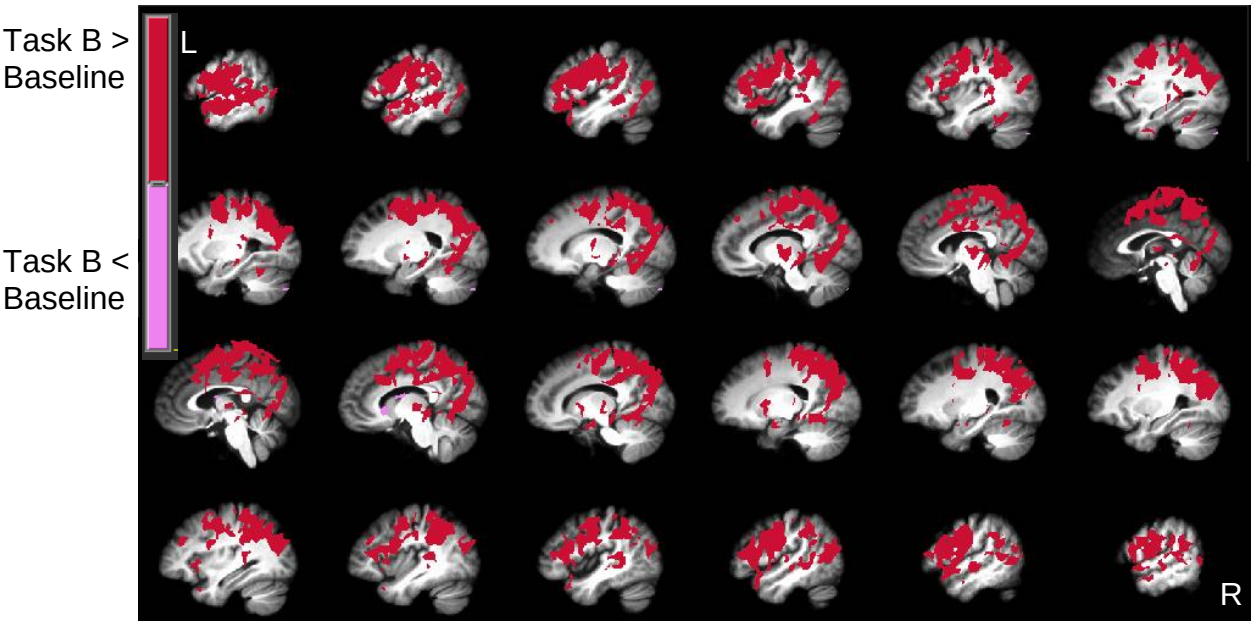
Young: Task B vs. Baseline



Old: Task A vs. Baseline

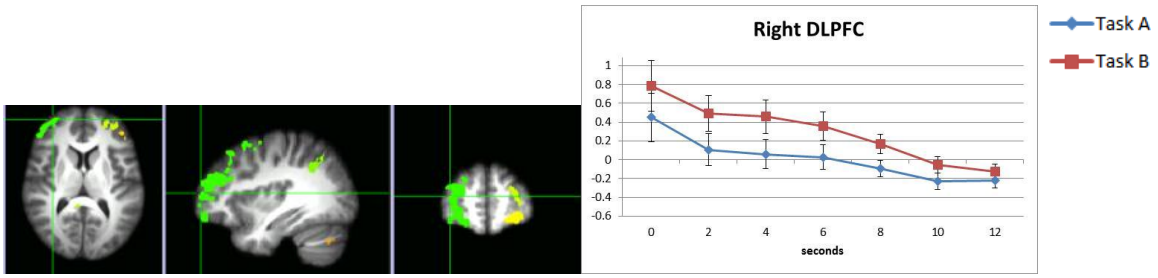


Old: Task B vs. Baseline



Effect of Inhibition (Task B vs. Task A) for Young (none for Old)

1



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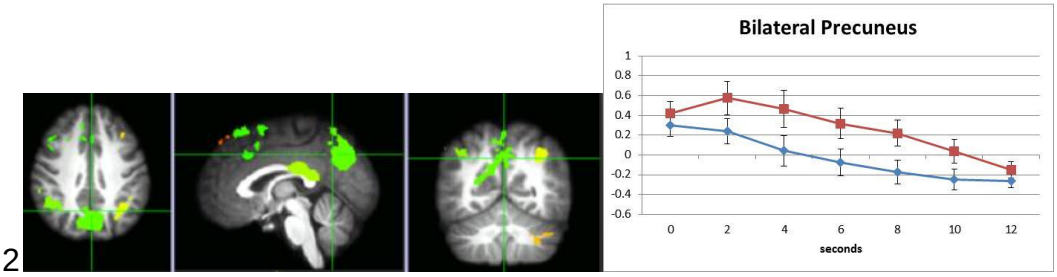

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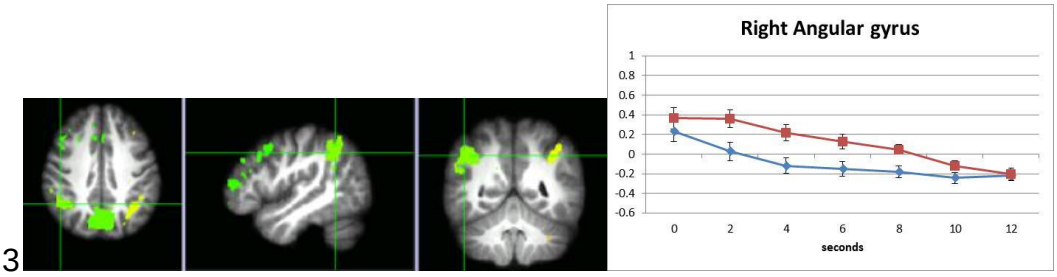

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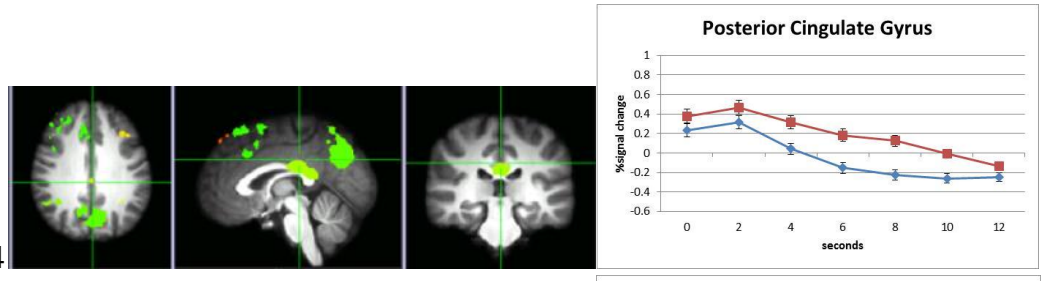

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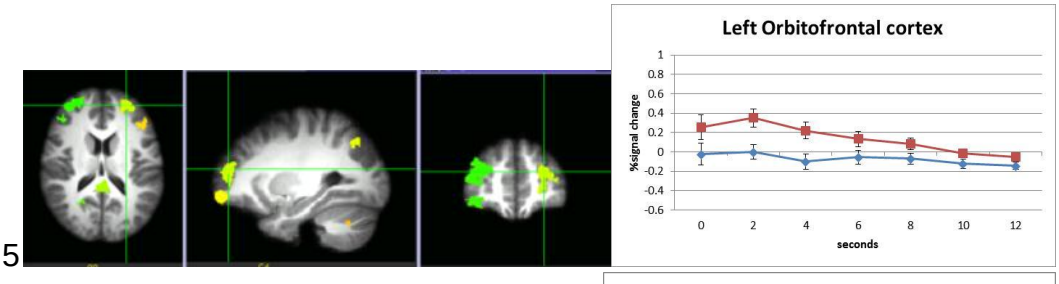

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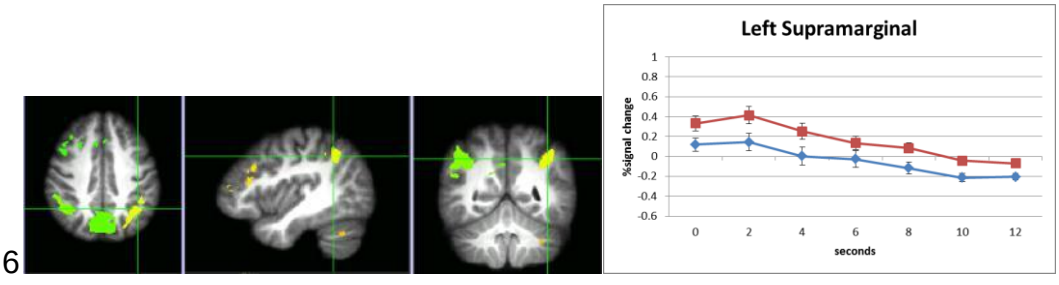

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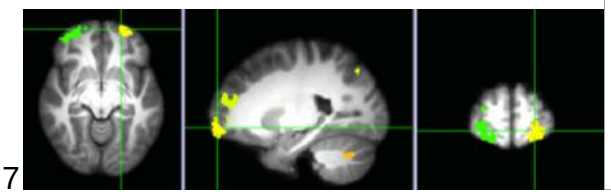
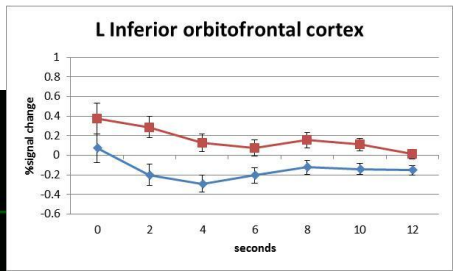
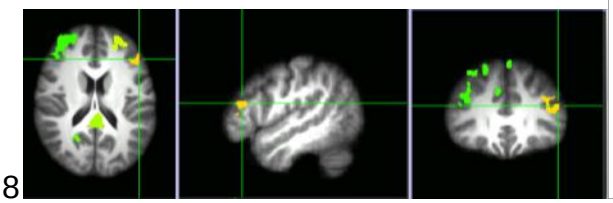
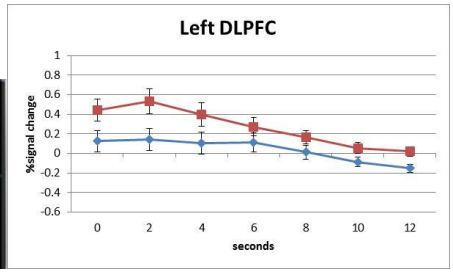


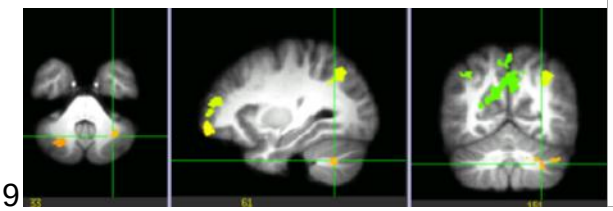

L Inferior orbitofrontal cortex
%signal change
seconds
Task A
Task B

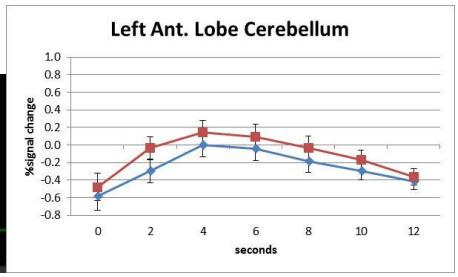
8



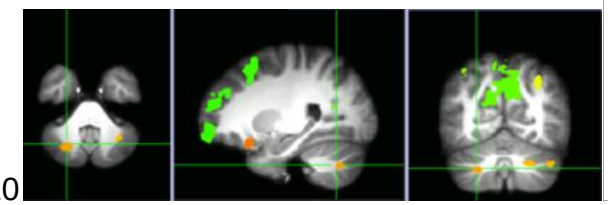

Left DLPFC
%signal change
seconds

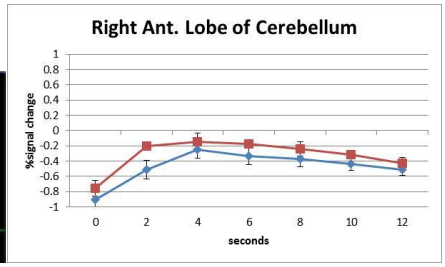
9



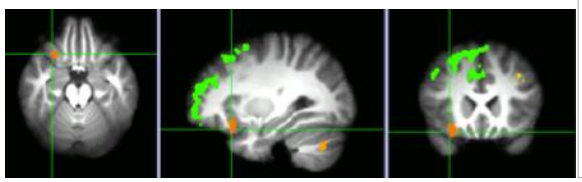

Left Ant. Lobe Cerebellum
%signal change
seconds

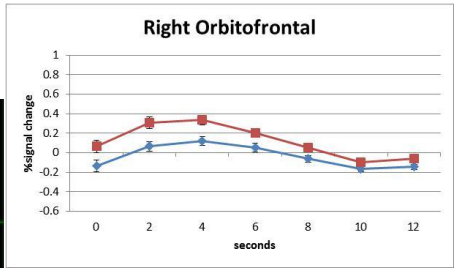
10



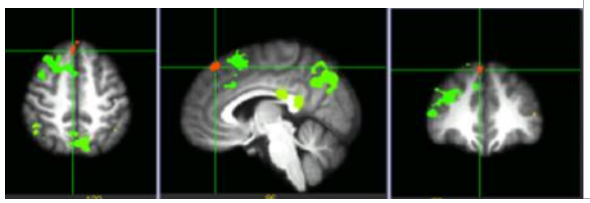

Right Ant. Lobe of Cerebellum
%signal change
seconds

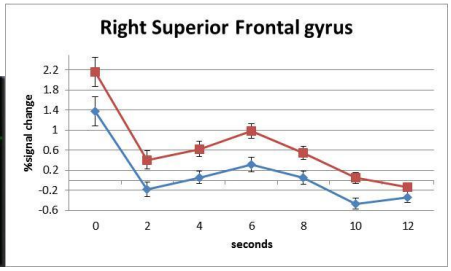
11




Right Orbitofrontal
%signal change
seconds

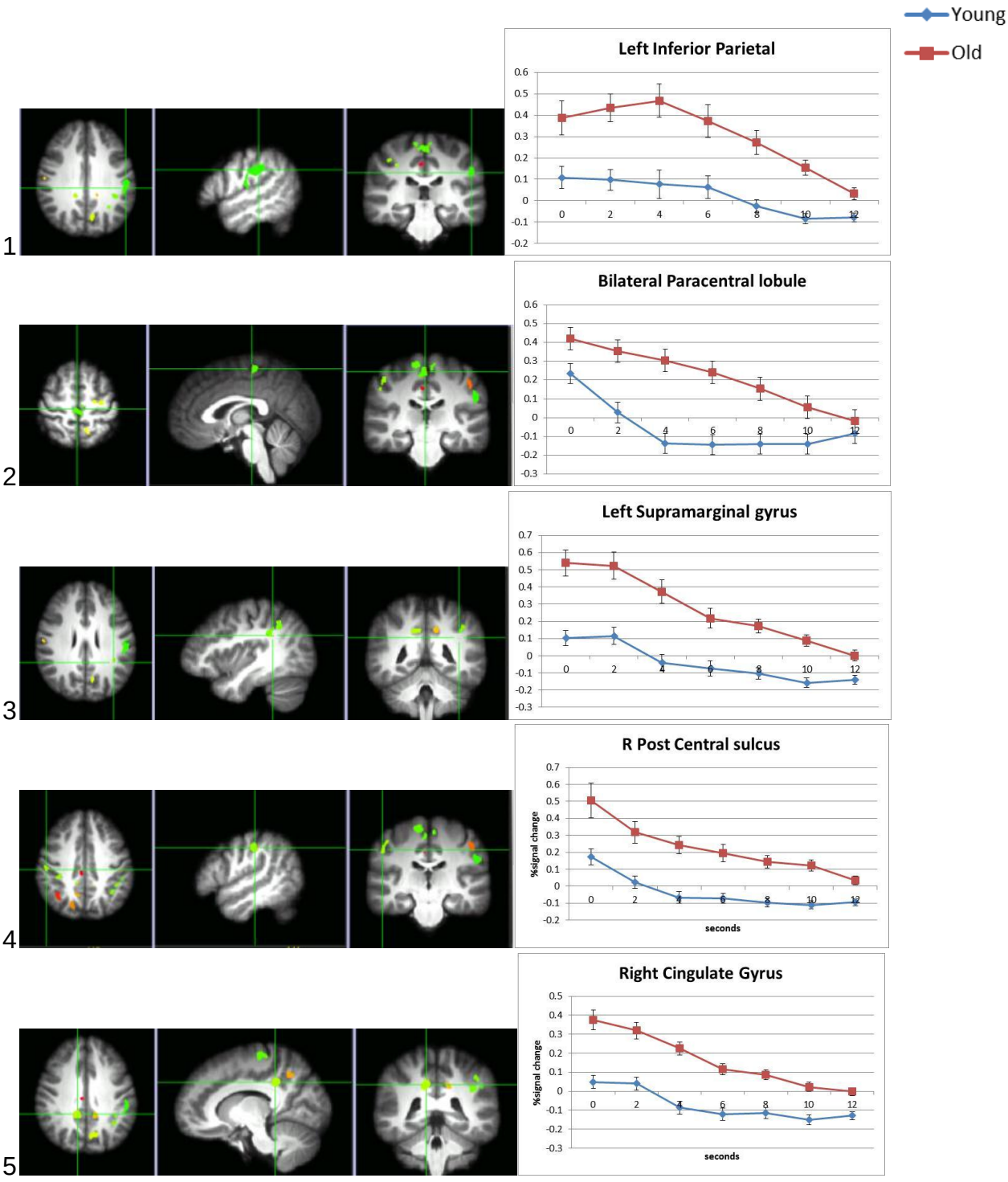
12



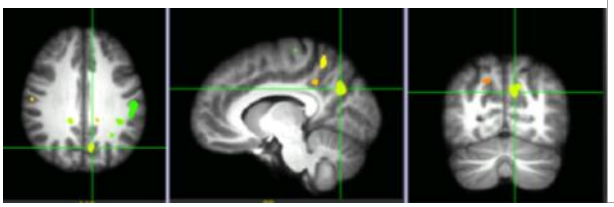

Right Superior Frontal gyrus
%signal change
seconds

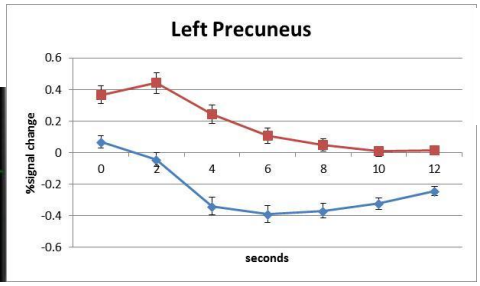
Effect of Age (Old vs. Young)

Task A (16 clusters)

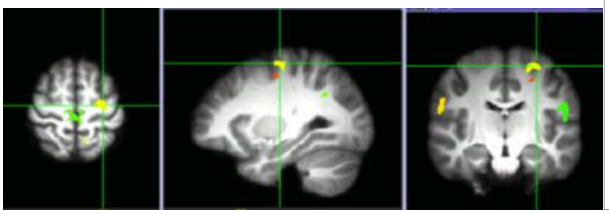


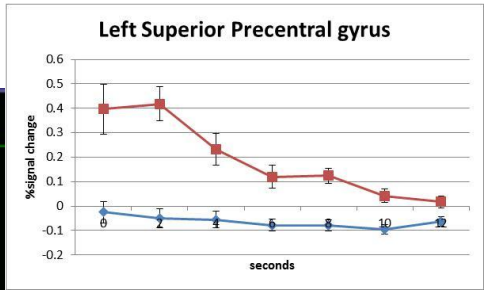
6



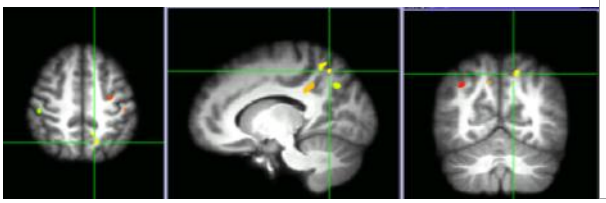

Left Precuneus
%signal change
seconds
Young
Old

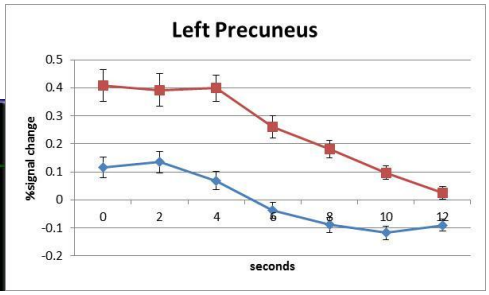
7



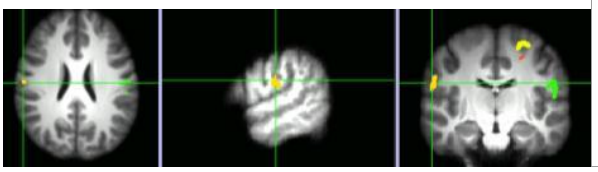

Left Superior Precentral gyrus
%signal change
seconds

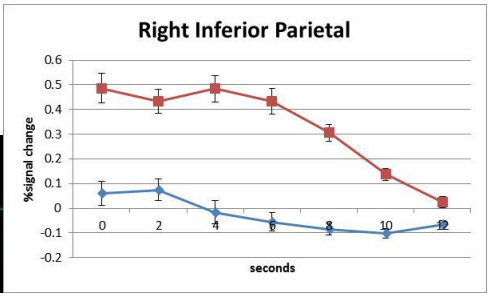
8



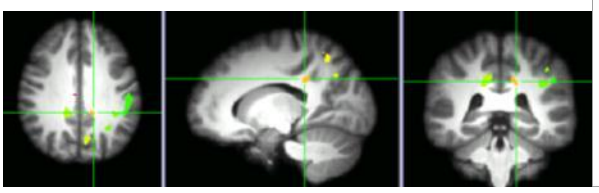

Left Precuneus
%signal change
seconds

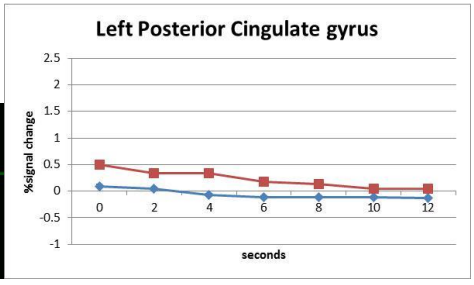
9



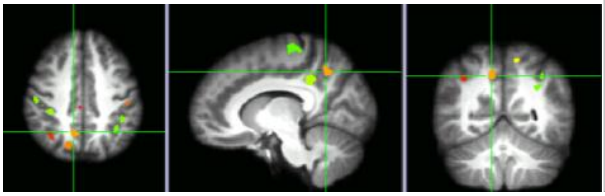

Right Inferior Parietal
%signal change
seconds

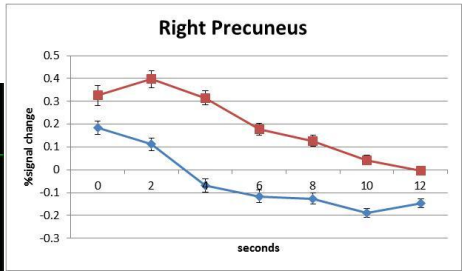
10



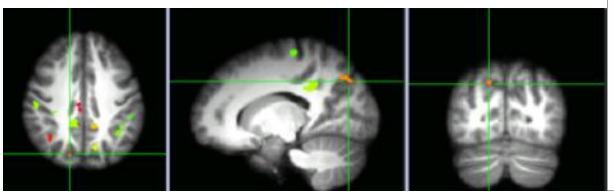

Left Posterior Cingulate gyrus
%signal change
seconds

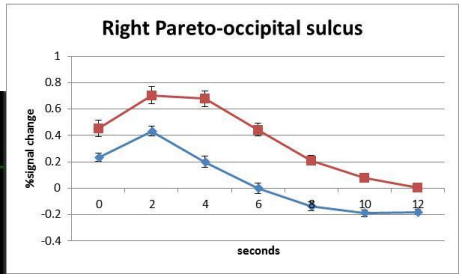
11

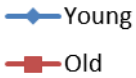



Right Precuneus
%signal change
seconds

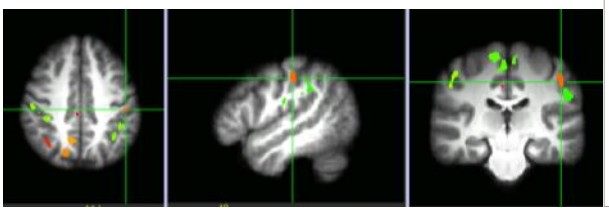
12

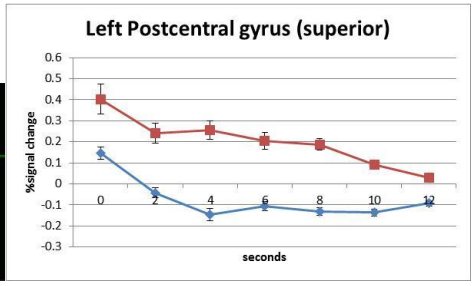



Right Pareto-occipital sulcus
%signal change
seconds
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0
2
4
6
10
12

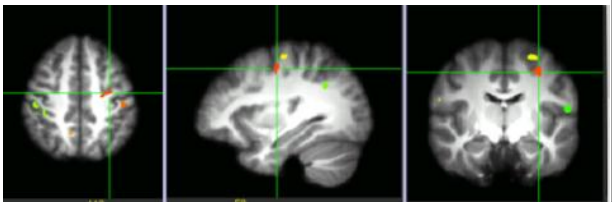

Young
Old

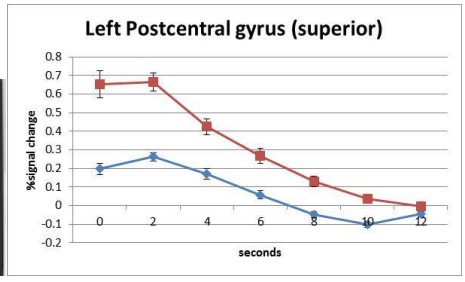
13



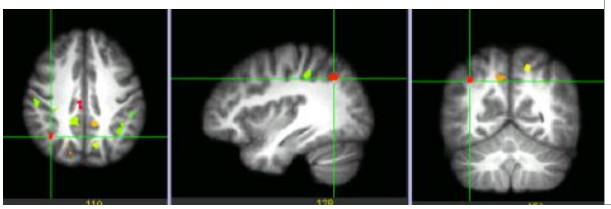

Left Postcentral gyrus (superior)
%signal change
seconds
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
0
2
4
6
8
10
12

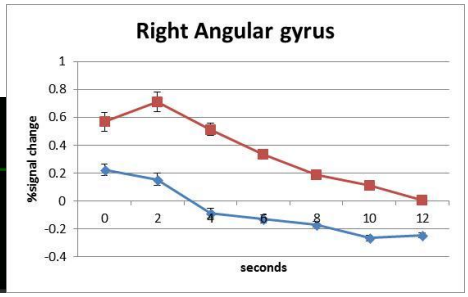
14



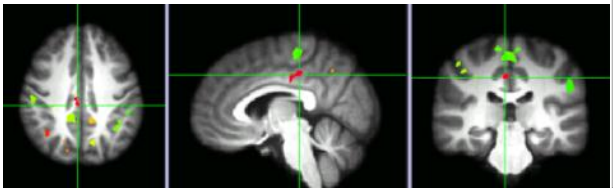

Left Postcentral gyrus (superior)
%signal change
seconds
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
0
2
4
6
8
10
12

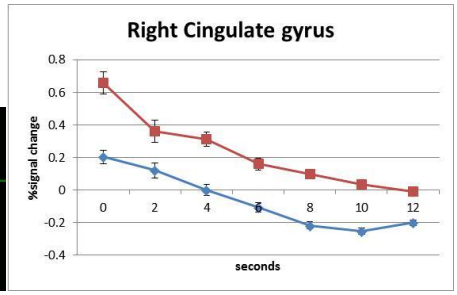
15



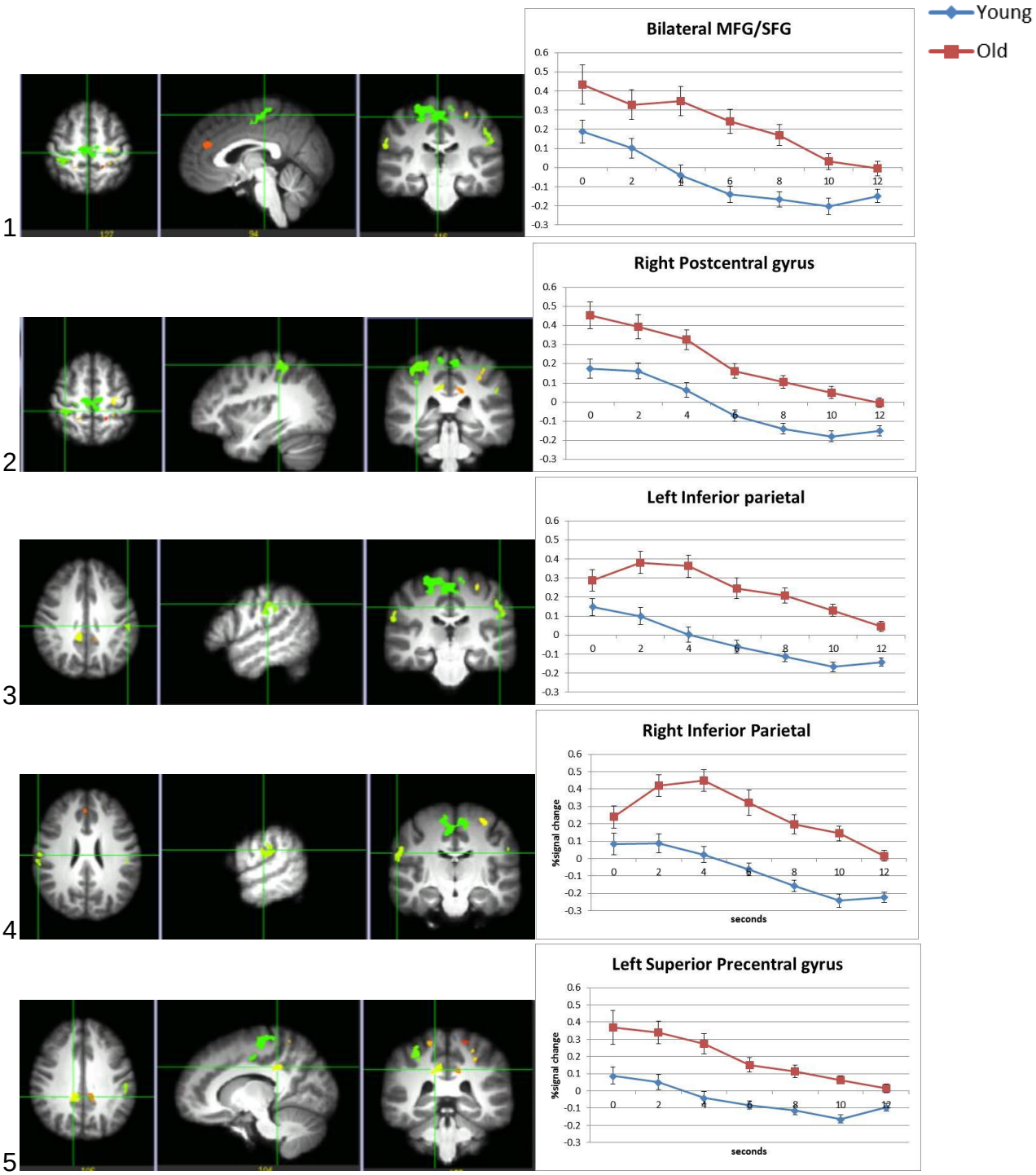

Right Angular gyrus
%signal change
seconds
1
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0
2
4
6
8
10
12

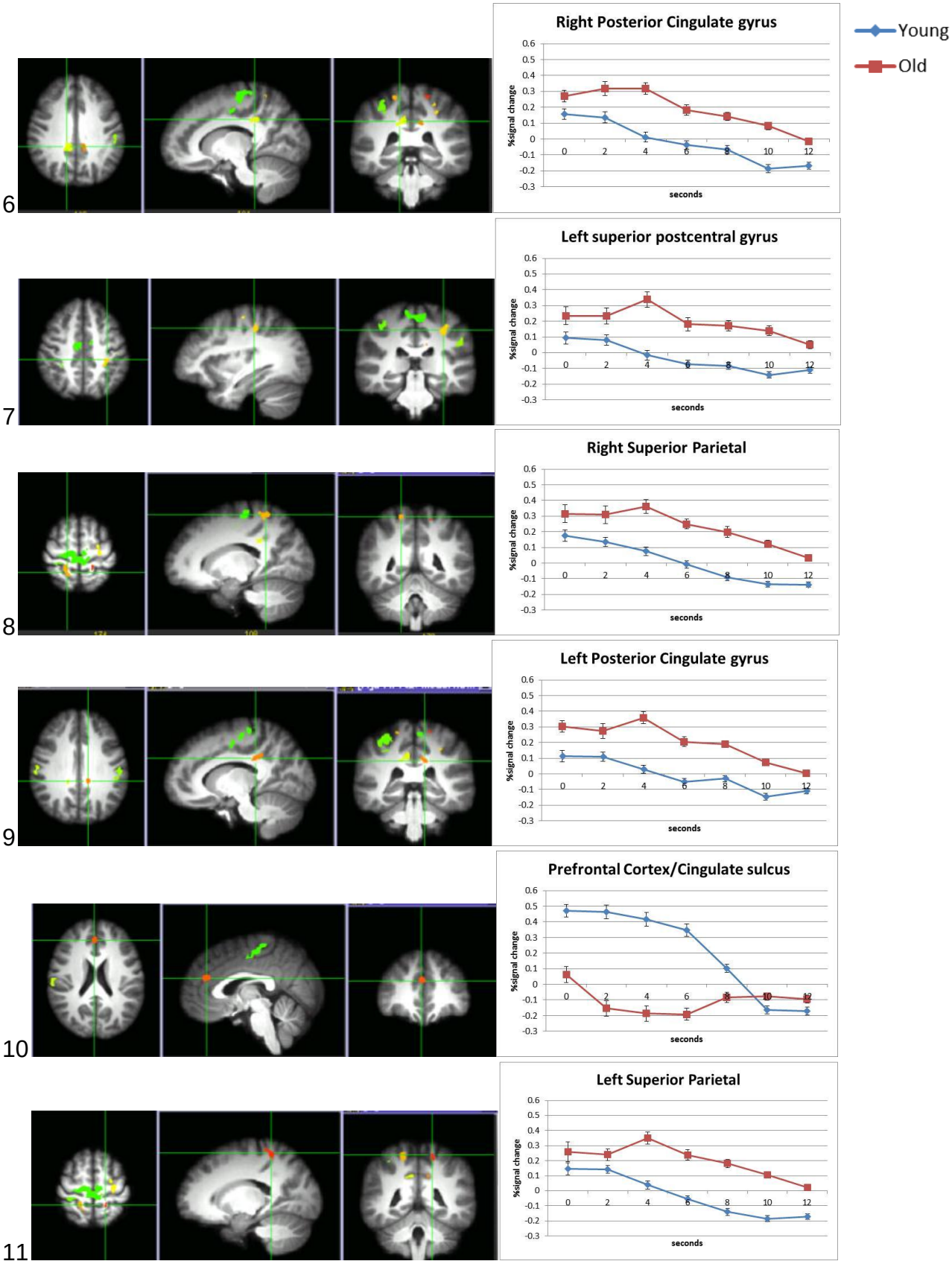
16



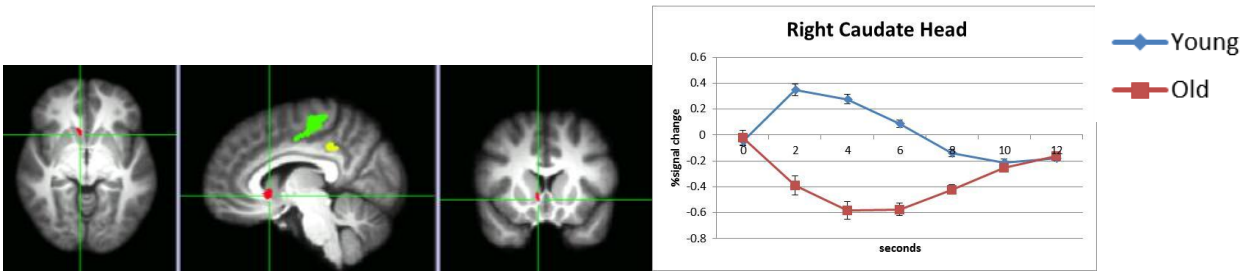

Right Cingulate gyrus
%signal change
seconds
0.8
0.6
0.4
0.2
0
-0.2
-0.4
0
2
4
6
8
10
12

Task B (12 Clusters)




Young
Old
6
Right Posterior Cingulate gyrus
%signal change
seconds
7
Left superior postcentral gyrus
%signal change
seconds
8
Right Superior Parietal
%signal change
seconds
9
Left Posterior Cingulate gyrus
%signal change
seconds
10
Prefrontal Cortex/Cingulate sulcus
%signal change
seconds
11
Left Superior Parietal
%signal change
seconds

12


Right Caudate Head
0.6
0.4
0.2
0
-0.2
-0.4
-0.6
-0.8
%signal change
0
2
4
6
8
10
12
seconds
Young
Old

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BIOGRAPHICAL SKETCH

Ilana Fawn Levy received her Bachelor of Arts degree in cognitive science from the University of Virginia (Charlottesville) in May 2003. Following graduation Ilana worked at the National Institutes of Mental Health in the Laboratory of Brain and Cognition from 2003 to 2005 after receiving a post-baccalaureate intramural research training award from the NIH. She received her Ph.D. from the Clinical and Health Psychology doctoral program at the University of Florida in 2012 with a concentration in clinical neuropsychology. While at UF, she worked in the Brain Imaging, Rehabilitation and Cognition lab under the mentorship of Bruce Crosson, Ph.D studying the neural correlates of language processing. Ilana completed her pre-doctoral Internship at the Boston Consortium through the VA healthcare system in Boston.