THE EFFECTS OF AGING ON COGNITIVE MOTOR CONTROL

Alex Shaver

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Director of Thesis: Dr. J.C. Mizelle

Major Department: Kinesiology

Introduction: Processing speed, working memory capacity, inhibitory function, and long-term memory are all aspects of information processing that change with age. Unsurprisingly, brain size, density, and proficiency regarding complex motor behaviors deteriorate with or without neurological disorders, illness, or injury. What remains unexplained is why declines in the understanding and execution of tool-related actions similar to clinical populations have been seen in the healthy aging population. However, some older individuals maintain the ability to plan and execute complex, goal-oriented movements, referred to as praxis. Whether praxis deficits are a product of neuroanatomical alterations or arise from changes in the functional properties of regions and networks normally recruited for processing tasks is currently unknown. We do know that older adults engage in scaffolding, overactivation of expected brain regions, or the additional activation of regions not typically recruited by younger adults in the same task. Whether or not these activation patterns are helpful or harmful in compensating for the inevitable changes with healthy aging is unclear. **Hypotheses:** We hypothesized that the older group (OG) would show increased bilateral activity compared to the younger group (YG) in response to the ideal tool (C1) and plausible tool (C2) conditions. This was expected to be true for each region of interest (ROI): frontal, premotor, and parietal. This bilateral activation and a shift from recruiting posterior brain regions to an anterior focus expected for C1 and C2 in OG. **Purpose:** This study aimed to better understand the cortical dynamics that support praxis in some healthy older by comparing their neural responses to younger adults. A better understanding of the differences

between these two healthy populations in successful tool-use and evaluation could help create more personalized and effective rehabilitation programs for clinical populations and otherwise healthy older adults. **Methods:** This study included 21 younger and 12 older right-handed participants between the ages of 18-35 and 60-84 years-old, respectively. Participants were presented with high resolution black and white images of ideal and plausible tool use to identify based on a preceding action description. Using a 64-channel electroencephalography cap, the neural responses of these individuals to the stimuli were recorded. 0-250ms and 350-550ms post stimulus onset over bilateral frontal, premotor, and parietal regions of interest (ROIs) for the C1 and C2 are reported. Variance was reduced using the Bootstrap resampling method and age-based comparisons of brain activation were made with non-parametric permutation-based statistics, $p < 0.05$. To account for false positives due to multiple comparisons, the false discovery rate was calculated and a corrected p-value ($q = .0143$) was used to determine statistical significance. **Results:** Overall, YG and OG had different approaches for evaluating ideal and plausible tools while error rate was essentially the same for both groups. C1 produced differences in the earlier processing stages in the left frontal, left premotor, and right parietal ROIs. In the same latency window, C2 produced differences in the same ROIs. During the later processing stages, C1 produced significant differences in all ROIs. C2 produced fewer differences in the same time window: the right frontal, both premotor, and right parietal ROIs. **Discussion:** The differences between YG and OG in C1 and C2 confirmed that healthy older adults employ bilateral and anterior activation patterns seen in the literature. Because OG had similar performance to YG, these activation patterns seem to be compensating for the increased difficulty and inefficiency of praxis related areas that accompany old age and here could be useful in creating effective rehabilitation programs.

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Alex Shaver

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by

Alex Shaver

APPROVED BY:

DIRECTOR OF
THESIS: _____
(Dr. J.C Mizelle, PhD)

COMMITTEE MEMBER: _____
(Dr. Nicholas Murray, PhD)

COMMITTEE MEMBER: _____
(Dr. Christine Habeeb, PhD)

CHAIR OF THE DEPARTMENT
OF (Put Department Name Here): _____
(Dr. Stacy Altman, PhD)

DEAN OF THE
GRADUATE SCHOOL: _____
Paul J. Gemperline, PhD

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Chapter I: Introduction

Everyday Tool Use

There are two components of everyday life that no one can avoid: tool use and aging. Fortunately, humans are able to preserve and refine tools and their associated usage across generations, promoting the modification and improvement of said tools. This is a unique skill when compared to most other species (Tomasello, 2002). While some similarities in tool-use behaviors exist among humans and other animals (Zuberbühler, 2002; Binkofski et al., 1999; Lefebvre, Nicolakakis, and Boire, 2002), humans prove far superior in their understanding of object characteristics and how other abstract variables, such as the ability to change object orientation, govern their relationships in the physical world (Johnson-Frey, 2003). Given time and this unique understanding, humans have begun optimizing tools for specific goals: a can-opener or a screwdriver. Using tools for their assigned job requires one to evaluate the context in which the behavior is to occur, evaluate the properties of the tools available, select the correct tool, then plan and execute the proper sequence of movements. The planning and execution of complex, goal-oriented movements is referred to as praxis. Because we learn to associate certain tools with specific jobs, a healthy individual would open their can of soup with a can-opener but would opt for a screwdriver to securely fix the last screw into a newly built wooden table. Eventually, this understanding allows one to use a tool successfully outside of the originally intended context. One would expect the same healthy individual would recognize that the screwdriver proves more useful than a toothbrush when opening a can of paint became the task. The ability to anticipate which action-sequence will produce the desired outcome during tasks requires an internal model of causal relationships between the characteristics of objects in question and the goal in mind. This understanding typically appears in early infancy of humans

and continues to be built upon through daily life experiences (Spelke, Breinlinger, Macomber, and Jacobson, 1992). Regardless of how early in life this seemingly trivial skill appears in humans, the associative deficit hypothesis points out that processes related to these high-level cognitive functions may be especially susceptible to the aging process. Most notably, aspects of relational/associative knowledge, defined here as how one understands the association between two objects, begin to deteriorate with age (Naveh-Benjamin, 2000).

Unsurprisingly, brain size, density, and our proficiency regarding tool-use deteriorate with the introduction of neurological disorders (e.g., apraxia), illness, and injury. What remains unexplained is why similar declines in tool-use performance have been seen in the healthy aging population (Zahr, Rohlfing, Pfefferbaum, and Sullivan, 2008; Naveh-Benjamin, 2000; Old, Naveh-Benjamin, 2008, Raz et. al, 2005). Performance deficits related to the present study appear as an inability to perform or comprehend skilled motor-related tasks, errors when recalling associative relationships between items (Wheaton and Hallett, 2007), and difficulty simulating future events based on past events (Addis, Wong, and Schacter, 2008). This could be a result of changes in the physical structure of the brain as praxis-relevant areas "experience accelerated tissue loss… that increases exponentially with advancing age" (Driscoll et al., 2009). Changes in the physiological brain activation strategies, including increased bilateral activation, are also well documented. It is unclear if this contributes to or counteracts problems in day-to-day tool-use in the elderly (Cabeza, Anderson, Locantore, McIntosh, 2002; Heuninckx, Wenderoth, and Swinnen, 2008). Fortunately, evidence suggests directed rehabilitation training of praxis motor behavior may slow age-related loss of praxis knowledge and may improve cognitive motor function. Further, training, exercise, and other interventions applied in older age or throughout the lifespan (Reuter-Lorenz, 2002) may increase available resources and

compensatory potential for all (Stern et al., 2005). Conversely, sleep deprivation, neurological damage, and genetic vulnerabilities may lower the resource ceiling, leading to under-activation and performance deficits. Regardless of the cause, aspects of information processing become less efficient with age: speed of processing, working memory capacity, inhibitory function, and long-term memory (Park and Reuter-Lorenz, 2009).

As these factors add up, understanding the appropriate context and manipulation of tools becomes harder for some individuals. At this point, whether context- or action-related processes are more affected by aging is not known but problems processing different aspects of tool-use can have profound effects on the quality of life. Whether the previously mentioned deficits are a product of neuroanatomical alterations or from changes in the functional properties of regions and networks normally recruited for processing tasks is also unknown. Related to these unknowns, compensatory scaffolding is described as the recruitment of additional circuitry with age. Scaffolding in the young brain is seen as a response to someone challenging their brain and is a large part of the learning process (Park and Reuter-Lorenz, 2009). Notably, scaffolding has been documented in healthy older adults (Cabeza, Anderson, Locantore, McIntosh, 2002). More specifically, hemispheric asymmetry reduction is a type of scaffolding seen in the older brain (HAROLD); (De Sanctis, et al., 2008). HAROLD activation patterns are described as a reduced activity in the initial region and increased activation in the same area of the opposite hemisphere – reminiscent of a mirror-image (Cabeza, 2002).

Overactivation is a change that also comes with aging. In the elderly, it has been found in association with poor performance. The dedifferentiation hypothesis states that the extra recruitment reflects an age-related difficulty in recruiting specialized neural mechanisms: the use of multiple and/or inefficient cognitive strategies, inhibition of a response, communication

between the left and right hemispheres declines, or dedifferentiation (Cabeza, Anderson, Locantore, McIntosh, 2002; Reuter-Lorenz and Cappell, 2008). Alternatively, the increases in bilateral brain activation and overactivation seen in this population could prove to be a compensatory response that helps counteract age-related neurocognitive decline. The compensation hypothesis implies that, even while performance is matched at the group level, overactivation across individuals should be correlated with higher performance in the older group. Although significant correlations may sometimes be lacking due to inadequate stimulus variability or a lack of statistical power, positive activation–performance correlations have been reported, lending support to the compensatory account of age-specific overactivations (Cabeza et al., 2004; Reuter-Lorenz and Lustig, 2005). In support of the compensatory hypothesis, several studies showed that HAROLD and an overall increase in activated areas correlated with better task performance in older adults (Park and Reuter-Lorenz, 2009; Heuninckx, Wenderoth, and Swinnen, 2008).

Compensatory or not, understanding these adaptations potentially helps explain deficits in successful maintenance of proper tool manipulation and context understanding with healthy aging. As the number of older adults in well-developed countries is expected to increase to 26% of the population by 2050, the need to understand mechanisms employed for successful maintenance of praxis knowledge and cognitive motor function throughout the lifespan becomes increasingly important for developing effective training programs (Bravo, Hertog, Kamiya, and Lai, 2015).

Purpose

As the percentage of the population over the age of 65 continues to rise, so does the need for effective training programs designed to recognize and slow age-related loss of praxis knowledge and improve cognitive motor function. Currently, it is unclear whether age-related performance deficits arise from neuroanatomical alterations or from more subtle changes in the functional properties of regions and networks used for (normally) routine processing tasks. How some of these individuals maintain their ability to understand tools and the different ways that they can be manipulated is also unclear. The purpose of this study was to better understand the cortical dynamics that support the ability of some healthy older adults to evaluate and plan complex motor sequences by comparing their neural responses to common tools in different situations to healthy younger adults.

Hypotheses

We hypothesized that the older population (OG) would show increased bilateral activity compared to the younger population (YG) in ideal (C1) and plausible (C2) tool-use scenarios. A shift from recruiting posterior brain regions to an anterior focus in OG was also expected during C1 and C2 compared to YG. This shift towards anterior and bilateral activity was determined by the absolute amplitude differences seen between YG and OG. We also expected to see differences between the groups' ERP amplitudes and latencies indicative of greater difficulty in OG compared to YG. The differences in the neural response patterns between these healthy populations highlighted differential activations related to everyday tool use as a function of healthy aging.

Chapter II: Review of Literature

Introduction

Tool-use is a fundamental component of daily life, making recognizing tools and understanding how they can or cannot be used crucial for normal functioning. In humans, this is accomplished through the communication of two visual processing streams. The ventral stream projects from primary visual cortex to the lateral and ventral surfaces of occipital cortex and through to the anterior ventral temporal cortex. This stream is responsible for mediating visual object recognition. This leaves object-directed action and spatial analysis largely to the dorsal stream (Goodale and Milner, 1992; Mishkin, Ungerleider, and Macko, 1983). This stream consists of the posterior parietal lobe, divided into inferior parietal lobe and superior parietal lobe by the intraparietal sulcus, the premotor cortex, middle frontal gyrus, inferior frontal gyrus, and posterior middle temporal gyrus (Buxbuam and Kalénine, 2010). In humans, the anterior intraparietal sulcus appears to encode the grasps afforded by an object, whereas the inferior frontal gyrus drives selection of object characteristics pertaining to the context (Rizzolatti and Matelli, 2003).

Unfortunately, these components and the behaviors they support are not always spared after injury, illness, or with healthy aging. The purpose of this study is to better understand the cortical dynamics that support proper tool-use in the healthy aging population to establish a foundation on which rehabilitation programs that better address deficits in performance can be based. This foundation will be based on the response of healthy young and healthy old brains to different tool-use scenarios. This chapter will review the current literature pertaining to aging and tool-use to better understand the previous findings.

Tool Recognition

While tool identification and manipulation are related, understanding the context in which a tool can be used and executing the movement sequence necessary differ. For example, posterior parietal and premotor activation in response to tools may be specialized to convey information related to the motor affordance of a tool rather than its identity (Jeannerod, Arbib, Rizzolatti, and Sakata, 1995; Johnson-Frey, 2004) while posterior and inferior temporal activation seems to be related to tool identification instead of the physical qualities of the tool (Martin, 2007). More specific information about motions associated with manmade, manipulable objects is thought to exist in the left middle temporal gyrus (Binkofski et al., 1999) and manipulable objects such as tools and utensils differentially activate the medial fusiform gyrus compared to living things (Chao et al., 1999; Noppeney et al., 2006). Even without movement or instructions to identify objects, viewing tools often elicits a response from inferior regions of the left intraparietal sulcus and ventral premotor cortex (Chao, Weisberg, and Martin, 2002).

When asked to identify tools, there is activation in the posterior and inferior temporal parts of the brain (Martin, 2007). High-order visual object recognition processes elicit activation in the fusiform gyrus and highly contextualized stimuli, such as large nonmanipulable objects, houses, and scenes, differentially activate the parahippocampal gyrus (Miceli et al., 2001; Downing et al., 2006). Class specific mechanisms for object recognition based on previous experience with tools have been seen to activate specific areas of the brain: left posterior middle temporal gyrus, left intraparietal sulcus, and left ventral premotor cortex (Chao, Weisberg, and Martin, 2002). The left middle temporal gyrus may store information about motions associated with specific manmade, manipulable objects (Binkofski et al., 1999). Additionally, goal-directed associative memory retrieval is thought to depend on top-down signals from the anterior

prefrontal cortex and medial temporal lobes (Ranganath, Cohen, Dam, and D'Esposito, 2004). Other studies have further investigated the temporal cortex and object representation, finding that anterior frontal regions, specifically the ventrolateral aspect of the prefrontal cortex, work with the temporal cortex to control sematic and associative memory in object representation (Ranganath, Cohen, Dam, and D'Esposito, 2004; Mayes, Montaldi, and Migo, 2007; Martin, 2007). Further, disrupted communication between the prefrontal and temporal regions due to lesions has been shown to impair visual associative memory (Tomita et al., 1999). Research has also highlighted the role of the lateral prefrontal cortex in retrieval and management of relevant information, response suppression, behavioral planning of temporal structures of actions and events, behavioral rule implementation, action selection and decision making, behavioral goal selection, reinforce based behavioral decisions, and strategic or conceptual behavioral planning (Tanji and Hoshi, 2008). Thus, the lateral prefrontal cortex plays an important role in the retrieval and understanding of requirements imposed by environmental alterations and in forming concepts that enable one to effectively deal with complex behavioral demands. This requires active maintenance of this visual information that is thought to be supported by activation of object representations in inferior temporal cortex (Ranganath, Cohen, Dam, and D'Esposito, 2004). Combined, we see that specialized mechanisms seem to link the identification of manipulable objects with information about the actions and context associated with their use.

Tool Manipulation

While deducing appropriate tool-object associations often involves using vision for accurate perception and action (Milner and Goodale, 2008), the "where" and "how" of tool-manipulation require the ability to process and react to many different types of sensory input.

Within the dorsal (parietal) stream, a network of primarily left-lateralized regions process object-associated motion (left middle temporal gyrus), online visuo-motor transformations for grasping objects (posterior parietal cortex), and the motor commands associated with tool use (inferior parietal lobule) (e.g., Culham et al., 2003, Beauchamp et al., 2002, Johnson-Frey, 2004). It has recently been proposed that the dorsal stream is actually subdivided into two streams, a "dorso-dorsal" (parietal) stream specialized for online control of grasping, and another, "ventro-dorsal" (temporal) stream specialized for skilled action and action recognition (Rizzolatti and Matelli, 2003). Damage to dorsal occipital and posterior parietal regions sometimes leads to impairment in object-directed grasping but leave object identification intact (Goodale and Milner, 1992). Damage to the left inferior parietal lobule can lead to similar impairments for using objects without negative effects on object identification (Johnson-Frey, 2004, Mahon and Caramazza, 2005). The dissociation of action (dorsal stream) and perceptual (ventral stream) visual processing suggests that tool-use errors present differently based on the type of error experienced.

Lesion studies highlight the importance of further processing and communication with other areas of the brain as disrupting communication between the prefrontal and temporal regions has been shown to impair the recall of visual associative information (Tomita et al., 1999). Precuneus activation has been shown to be involved in the recall of memory related visual information (Cavanna and Trimble, 2006) and may help construct accurate visuospatial representation based on the functionally appropriate hand-tool interaction needed for successful tool manipulation (Vingerhoets, 2008). Internal representation of actions and actual movement strategies involved in tool manipulation have been seen in the posterior parietal cortex (Creem-Regehr, 2009). This tool-specific response remains true even when participants recognized

graspable objects without any actual movement (Hattori et al., 2009). Activation of object representations, either through working memory maintenance or associative long-term memory retrieval, was supported by sustained activity within category-specific inferior sub-regions of the temporal lobe and within lateral parietal and frontal cortex sub-regions (Ranganath, Cohen, Dam, and D'Esposito, 2004). The hippocampus was also seen to be disproportionately recruited with the anterior parietal and frontal regions of the brain during associative long-term memory retrieval suggesting that these regions may directly encode the associative memory used to guide behavior (Miyashita and Hayashi, 2000).

Tool-related responses found in the left premotor and left posterior parietal cortices (Chao and Martin, 2001) may represent stored information about object use-associated motor patterns, as these areas have previously been implicated in motor imagery and control (Grady et al., 1994; Jeannerod et al., 1995; Nyberg et al., 1996; Binkofski et al., 1999). Laterality differences related to matching and mismatching responses for both tool and environmental images when compared with controls consistently showed differences in activation of the left hemisphere. (Mizelle and Wheaton, 2010). They also showed activation of the left superior parietal lobule during hand manipulation of three-dimensional objects regardless of the hand used (Binkofski et al., 1999).

Apraxia

Although knowledge of correct tool use likely involves parietal and temporal regions, the dissociation of action (dorsal stream) and perceptual (ventral stream) visual processing suggests that these mechanisms may represent tool-use errors differently, based on whether the error is in context or usage (Mizelle and Wheaton, 2010). For a neurotypical individual, identifying correct and incorrect tool use is straightforward. People that have experienced injury or illness often see

declines in their ability to comprehend the same tool-use scenarios compared to their healthy counterparts. For example, damage to the ventral stream can lead to problems identifying objects presented visually while normal object-directed action remains intact. Damage to dorsal-occipital and posterior parietal regions can lead to impairments in object-directed grasping while leaving the ability to identify objects unaffected (Goodale and Milner, 1992). Damage to the left inferior parietal lobe can result in impairments using objects, despite being able to identify the object (Johnson-Frey, 2004; Mahone and Caramazza 2005). In stroke patients, the presence of cognitive and performance deficits affecting perception and control of action seems to be more prominent in patients that have suffered damage to the left parietal or posterior frontal lobe compared to controls and patients with damage to those areas in the right side of the brain. The people with damage to the right side of the brain still produced errors or were much slower compared to controls but it was more likely that those errors were related to visuospatial processing issues (Sunderland et al., 1999). Still, all are processes that, if affected, make decisions involving tool-use context and manipulation difficult.

Apraxia is the term used to describe a variety of phenomena involving the inability to program the motor system to perform or comprehend skilled motor-related tasks (Wheaton and Hallett, 2007). Conceptual apraxia is defined here as the inability to select and use tools and utensils despite maintaining normal sensation, motor function, and coordination (Moll, De Oliveira-Souza, De Souaz-Lima, Andreiuolo, 1998). This inability to access knowledge related to the correct function of objects is thought to be at least partially attributed to lost visual sensory information (Ochipa, Rothi, and Heilman, 1989). Because conceptual knowledge of the tool is lost in this type of apraxia, one might try to comb their hair with a toothbrush or try writing with a screwdriver as if it were a pen (Sathian et al., 2011; Gross and Grossman, 2008). Essentially,

those with conceptual apraxia misunderstand the "what" of a tool but can comprehend the "how".

Ideomotor apraxia, however, is a disorder traditionally characterized by deficits in properly performing tool-use pantomimes and communicative gestures (Wheaton and Hallett, 2007). So, conceptual knowledge of the tool is maintained but the ability to understand how the mechanical properties of the tool relate to its function in the physical world or the motor representation of the tool are lost. Meaning, a person with ideomotor apraxia would know that a toothbrush is the best choice to brush their teeth, but they have lost the motor representation of how to use it. Unlike someone with conceptual apraxia, in ideomotor apraxia the "what" is maintained but the "how" is lost. These issues occur in injured and diseased populations and potentially in otherwise healthy older individuals, impacting daily functioning and quality of life (Donkervoort, Dekker, and Deelman, 2006). Because both heathy and impaired populations are affected, understanding praxis representations and the mechanisms of formation, storage, and recall of tool-related knowledge is a necessary precursor to designing effective approaches to neurological rehabilitation of the apraxias (Buxbaum, Kyle, Grossman, and Coslett, 2007; Wheaton and Hallett, 2007).

Aging

In the human brain, physical, morphological, and functional changes are expected to accompany the healthy aging process. This is particularly true for areas related to praxis (Driscoll et al., 2009). As these changes occur, actions tend to slow and errors begin to resemble those seen in populations with brain injury or disease when neither are present (Zahr, Rohlfing, Pfefferbaum, and Sullivan, 2008; Naveh-Benjamin, 2000; Old, Naveh-Benjamin, 2008). Errors related to processes involved in understanding tool-context and tool-manipulation, also become

common (Chen, Myerson, and Hale, 2002). Unfortunately, which of these processes is more vulnerable to aging is complicated for a few reasons. First, there is an extremely wide range of possible actions to be studied that are associated with different processing demands depending on how they are elicited. This problem is exaggerated by the use of different patient populations, lesion sizes, praxis tasks, criteria for defining apraxia, means of error assessment, and imaging techniques throughout research (Petreska, Adriani, Blanke, and Billard, 2007; Gross and Grossman, 2008).

Anatomically, age related changes include decreases in density, volume, and overall brain size (Zahr, Rholfing, Pfefferbaum, and Sullivan, 2008; Raz et al., 2005). In the cortex, significant declines in cortical volume and grey matter thickness have been reported in middle and superior frontal, inferotemporal, prefrontal, and entorhinal cortices (Raz et al., 2005; Hutton, Draganski, Ashburner, and Weiskopf, 2009; Driscoll et al., 2009). Declines in the white matter integrity of parieto-frontal connections (Davis et al., 2009) and volume of frontal fiber tracts (Zahr, Rohling, Pfefferbaum, and Sullivan, 2008) with age are well documented. Connections between the orbital, medial, and lateral frontal areas and the superior temporal gyrus also seem to be compromised (Lu et al., 2002). Typically, these physical changes are accompanied by performance impairments in cognitive and motor tasks comparable to impaired populations (Mahon et al., 2007; Damasio et al., 2004).

Differences in the functional properties of the aging brain are seen in various tasks including motor preparation and execution (Sterr and Dean, 2008; Heuninckx, Wenderithm and Swinnen, 2008), visual memory (Dennis, Kim, and Cabeza, 2007), and sensory processing (De Sanctis et al., 2008). Problems in relational and associative processes (Cabeza, 2006; Naveh-Benjamin, 2000) also commonly accompany old age. Apraxia is common in many diseases more

likely to affect the older population. Such diseases include dementia, Huntington's disease, corticobasal ganglionic degeneration, and occasionally in Parkinson's disease. Apraxia is also common in Alzheimer's disease, but is rarely described as a presenting symptom. Interestingly enough, it has presented in older individuals without any known disease or injury (Green et al., 1995; Okuda et al., 1992). Associated with these deficits, we see older adults recruiting additional brain regions when compared to their younger counterparts while performing motor tasks.

This additional neural recruitment is termed “dedifferentiation” or “scaffolding” and can take multiple forms (Park et al., 2001; Park and Reuter-Lorenz, 2009). These changes are usually, but not always, associated with better performance in older adults when compared to those that do not show the same changes (Park and Reuter-Lorenz, 2009; Heuninckx, Wenderoth, and Swinnen, 2008). The dedifferentiation hypothesis states that the extra recruitment and overactivation reflect age-related difficulty in recruiting specialized neural mechanisms, such as inhibition or the use of multiple and/or efficient cognitive strategies (Cabeza, Anderson, Locantore, McIntosh, 2002; Reuter-Lorenz and Cappell, 2008). However, it is possible that inadequate variability or a lack of statistical power sometimes leads to a lack of statistically significant correlations between better performance and age-specific overactivations (Cabeza et al., 2004; Reuter-Lorenz and Lustig, 2005). Instead, the compensation hypothesis predicts that overactivation across individuals should correlate with higher performance in the older group even while performance is matched at the group level.

Increased bilateral activation is one pattern of dedifferentiation particularly common in healthy older adults. More specifically, hemispheric asymmetry reduction (HAROLD) is a type of dedifferentiation commonly adopted by the older brain (De Sanctis, et al., 2008). HAROLD

activation patterns are described as a reduced activity in the primary region of one hemisphere and increased activation in the same area of the opposite hemisphere, reminiscent of a mirror-image (Cabeza, 2002). A shift from utilizing posterior brain areas to anterior areas with changes in visual processing (PASA) (Davis et al., 2008; De Sanctis et al., 2008) is another dedifferentiation pattern well documented in older adults.

In support of the compensation hypothesis, greater anterior frontal activations, despite largely intact perceptual mechanisms in posterior areas, are seen in more successful older individuals during recognition memory tasks (Grady et al., 1994). In other words, older adults typically show increased bilateral prefrontal activation during recognition memory compared to younger counterparts. To test the relevance of this pattern, some studies have used transcranial magnetic stimulation (TMS). TMS is a technique that applies a series of focally directed magnetic pulses to the scalp to stimulate the underlying neural tissue. TMS can be applied in either a deactivating or an activating mode. In the deactivating mode, TMS temporarily disrupts the underlying neural tissues enough to produce a virtual lesion. When used in the activating mode, TMS increases the contribution of the underlying tissue.

Rossi et al. (2004) used TMS to deactivate either hemisphere in some older and younger individuals. They found that regardless of the hemisphere that was deactivated, older individuals were impaired during the memory task. In contrast, the younger adults were only significantly impaired when TMS was applied to their left hemisphere. This suggested that recognition does relies on both hemispheres for older individuals. In another line of work, memory improvement was demonstrated in older adults after using TMS in the stimulating mode to prime the underlying prefrontal circuitry. When TMS was applied prefrontally, a group of low-performing elderly showed improvement. Functional magnetic resonance imaging (fMRI) showed their brain

activation to be unilateral before TMS and bilateral after TMS, in association with their improved performance (Sole-Padulles et al., 2006). These results contribute to the idea that the increases in bilateral brain activation and general overactivation seen in this population could prove to be a compensatory response designed to help counteract age-related neurocognitive decline and maintain cognitive function (Park and Reuter-Lorenz, 2009; Cabeza, Anderson, Locantore, McIntosh, 2002).

Electroencephalography and the Event Related Potential

The average human brain has about 86 billion neurons (Herculano-Houzel, 2009), and the communication between them is the key brain activity. Thankfully, encephalography (EEG) is a noninvasive and relatively cost-effective way to quantify and better understand this activity. EEG records of the summed electrical activity of neurons using electrodes placed on the scalp. More specifically, EEG measures postsynaptic potentials that are influenced by a number of neurotransmitter systems and generally happen slow enough to be reliably measured (Da Silva, 2010). These voltages are produced when neurotransmitters bind to the receptors on the membrane of the postsynaptic cell, making ion channels open or close. The change in electrical charge outside the membrane lasts in the extra-cellular space for up to 200ms. The extra-cellular electrical charge, positive or negative, is what is measured by the electrodes on the scalp. The dendrite at the top of a pyramidal cell is positive or negative depends on two factors. First, whether an inhibitory or excitatory stimulus has come to the synaptic junction from the axon of another cell and, second, whether that synapse is proximal or distal to the cell body. For example, if an excitatory stimulus comes in near the distal end of the dendrite (near the surface of the cortex) the change in permeability of the membrane allows Na^+ to rush into the cell at that point leaving the extracellular space negative. The extra-cellular space at the

opposite (proximal) end of the dendrite will be positive. The EEG thus represents the sum of excitatory and inhibitory postsynaptic potentials (Beres, 2017).

EEG plays a crucial role in many aspects of today's research. It is used in medicine, to monitor brain activity and has been used to diagnose brain death in patients. It has been used to study how damage from a stroke or head trauma, epileptic activity, and sleep disorders impact different populations and evaluate the effectiveness of different treatment interventions. In other research, it is useful in investigating various cognitive functions, such as memory or attention. One popular method in EEG is the evaluation of time-locked stimulus responses called event-related potentials (ERPs).

An ERP is a measured brain response with a fairly predictable waveform that allows for the visualization of cognitive processes directly resulting from a stimulus. ERP waveforms are commonly characterized by "components" that are denoted by the latency and amplitude of the positive and negative voltage deflections. Most components are referred to first, by a letter (N/P) indicating polarity (negative/positive). This is generally followed by a number indicating either the latency in milliseconds or a sub-component's position in the waveform. For example, P300 is an ERP component that is an expected positive peak anywhere between 250ms to 700ms post stimulus onset. This peak is often reported as P3a and P3b. This is because some sub-components seem to be significantly different in different populations and between different types of stimuli. Generally, these positive peaks follow earlier negative deflections, such as N100 which is ~100ms post stimulus onset.

Almost all studies have found age-related delays in the latency of ERP components thought to be related to response time, cognitive control, response inhibition, and understanding,

such as P300, P400, and N400 (Bennett et al., 2004; Dirnberger, Lang, and Lindinger, 2010). ERP amplitudes, however, are less consistent in regards to age. An increased contingent negative variation (CNV) amplitude in old compared to young participants was found in some studies (Hillman et al., 2002). Other studies report a reduction of CNV amplitudes in older participants (Dirnberger et al., 2010). The latter being seen more specifically in CNV amplitudes over the frontal areas with no change in parietal areas (Wild-Wall et al., 2007). Still, some studies have reported no group differences in these areas (Bennett et al., 2004). In older subjects, the N2d and P3d-NOGO waves are generally smaller in amplitude compared to younger adults (Bennett et al., 2004), with at least one study reporting the opposite finding (Hong et al., 2014).

Summary

In summary, this review demonstrates the importance of gaining a better understanding of the healthy aged brain as it is related to everyday tool use. Understanding the basic mechanisms of decline in praxis-relevant brain regions could have a significant impact on our ability to better maintain quality of life for the growing aging population, as well as aid in the development of neuro-rehabilitation programs. To effectively map the healthy aging process, EEG was used to determine potential differences between healthy younger and healthy older individuals' responses to different tool use scenarios.

Chapter III: Methods

Introduction

The areas of the brain related to praxis are physically and functionally known to be more susceptible to the wear-and-tear of aging. Additionally, problems with relational memory often increase with age even without the presence of injury or disease. However, some healthy individuals are able to maintain skills that use relational memory, such as tool-use, throughout their lifespan. We hoped to better understand the neural mechanisms adopted by healthy older individuals that have maintained comprehension of tool-object associations and motor function. To accomplish this, EEG was used to compare the neural response patterns of older and younger healthy individuals to different tool-use scenarios. EEG measures electrical potential differences at the synapses of the cell membrane of neuronal excitatory post-synaptic potentials (EPSP) (Olejniczak, 2006) using electrodes. The electrodes are placed on the surface of the scalp with their positions based on anatomical landmarks correlating with underlying brain regions (Jasper, 1958). Because of this, EEG can efficiently record the electrical signal (voltage) of the brain as a function of time. This allows for the interpretation of brain function and activity through ERPs. The present study investigated some of the ERP components thought to index action perception and understanding. The differences seen within two latency windows: 100-250ms post-stimulus onset and 350-550ms post-stimulus onset over bilateral frontal, premotor, and parietal regions. A better understanding of the complex relationship between these components in healthy older and younger adults potentially explains how some healthy older individuals are able to maintain their ability to properly evaluate and execute tools over their lifespan.

Participants

Healthy younger and older individuals were recruited to participate in this study. Each participant was presented with the University and Medical Center Institutional Review Board of East Carolina University approved informed consent and procedures for testing prior to participation. This study included twenty-one younger (YG) and twelve older (OG), right-handed participants. Handedness was determined by the Edinburgh Handedness Inventory (Oldfeild, 1971). Healthy was defined as having no current or previous neurological pathology which would interfere with the ability to view pictures, comprehend the use of tools, physical pathology which may result in altered cortical representation of tools or their associated objects, or presence of systemic disease that alters ability of subjects to participate in activities of their choice. The younger group was between 18 and 35 years old and the older group between ages 60 and 84 (Table 1). Specific exclusion criteria included 1) a history of stroke or neurodegenerative disease, 2) upper extremity neuromuscular pathology, 3) upper extremity orthopedic pathology, and 4) ocular or neurological abnormalities that impact visual function.

Demographics		
Group	Younger	Older
Sex	11 F; 10 M	8 F; 4 M
Age (yrs)	22 (± 4)	75 (± 9)

Table 1: Average (± sd)

Task

SuperLab (Cedrus, TX, USA) and Curry 7 (Compumedics Neuroscan, NC, USA) were used to present stimuli and collect data. The stimuli consisted of high resolution black and white images in one of six categories: ideal tool (e.g., using a whisk to whisk eggs), incorrect context

(e.g., using a hammer to whisk eggs), incorrect manipulation (e.g., holding a whisk on the wrong end), plausible tool (e.g., using a fork to whisk eggs), a lone hand, or a lone tool. Each trial started with a text prompt explaining the intended action-oriented goal (e.g. "Whisk eggs"). This was followed by a black-and-white circle followed by a black fixation-cross, warning the subjects that the trial is about to begin. A blank white screen appeared for a pseudorandom amount of time between one and four seconds before the picture to avoid any kind of expectancy effect. The stimuli were displayed until the participant selected their answer using the response pad or four seconds had passed (Figure 1).

Before beginning the experiment, participants received instructions to identify the stimulus type of the black-and-white images by pressing a button on a SuperLab response pad that corresponded to one of the six previously mentioned stimulus types. The response pad sent a matching event marker to Curry 7 that indicated the participants response. SuperLab software sent an event marker to note stimulus type and time of onset. To familiarize participants with the response pad and confirm understanding of the stimuli, a practice round with 2 examples of each stimulus type was completed before the start of the first block of stimuli. For the experiment, participants were asked to complete a total of 9-12 blocks of 10-15 pictures. Total, 100 stimuli responses were recorded. The participants had built in breaks between blocks to rest that they may have chosen to skip.

Data Collection and Analysis

EEG signals were collected using a 64-channel sintered NeuroScan electrode cap and SynampsRT amplifier with Curry 7 software interface (NeuroScan, Compumedics, Charlotte, NC). EEG data were marked in Curry for event-onset and category as presented through the Curry-SuperLab interface. Raw data files were imported into MATLAB

(Mathworks, Natick, MA) to be processed and analyzed using a proprietary processing script utilizing EEGLAB (Delorme and Makeig, 2004). ERPs are known markers of brain activity in the time-voltage domain with a fairly predictable shape, amplitude, and latency that follow the onset of a stimulus (Mizelle and Wheaton, 2010). For each stimulus type, EEG data from the two populations over frontal, motor, temporal, parietal, and occipital regions in both hemispheres was collected. The two stimulus types being reported in the present study are "ideal tool" (C1) and "plausible tool" (C2). Additionally, activity within two latency windows was evaluated: an early component (L1; 0.1s-0.25s) and a late component (L2; 0.3s-0.7s). These were chosen because they allow the earlier, perception aspects of processing to be examined along with the later, more cognitive components (Sur and Sinha, 2009).

Before the recorded EEG activity could be evaluated, a high pass filter (1 Hz) was applied followed by a low pass filter (30 Hz). Data were then sorted into epochs consisting of information from 1000ms before stimulus onset through 3s after, which did include the warning cue and the full duration of the stimulus. Time zero (0ms) is related to the beginning of the epoch- the previously mentioned event-onset. Each epoch was baseline corrected with the interval from -1000ms to -250ms. From there, the event related potentials (ERPs) were averaged across trials over individual participants then a grand average was computed for each region of interest (ROI; Figure 2). Variance was reduced using the Bootstrap resampling method. For this, epochs were randomly selected (with replacement) and averaged for every participant 1000 times, and these were then averaged to represent subject-specific activations. The number of epochs selected per repetition was identical to the number of epochs present for each individual participant and condition. Age-based comparisons of brain activation were then made with non-parametric permutation statistics based on the Monte Carlo resampling technique with α set at

0.05 (Maris and Oostendveld, 2007). To account for false positives due to multiple comparisons, the false discovery rate was calculated and a corrected p-value (q = .0143) was used to determine statistical significance (Benjamini and Hochberg, 1995) (Table 3).

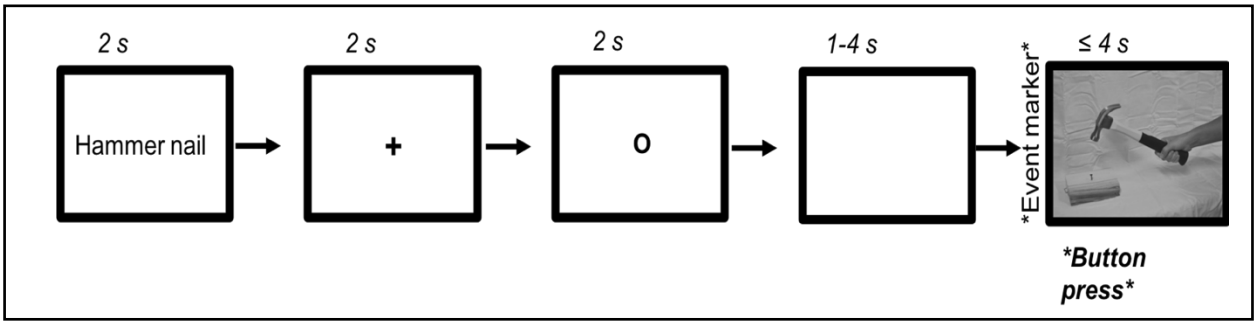

Figure 1: Stimulus example.

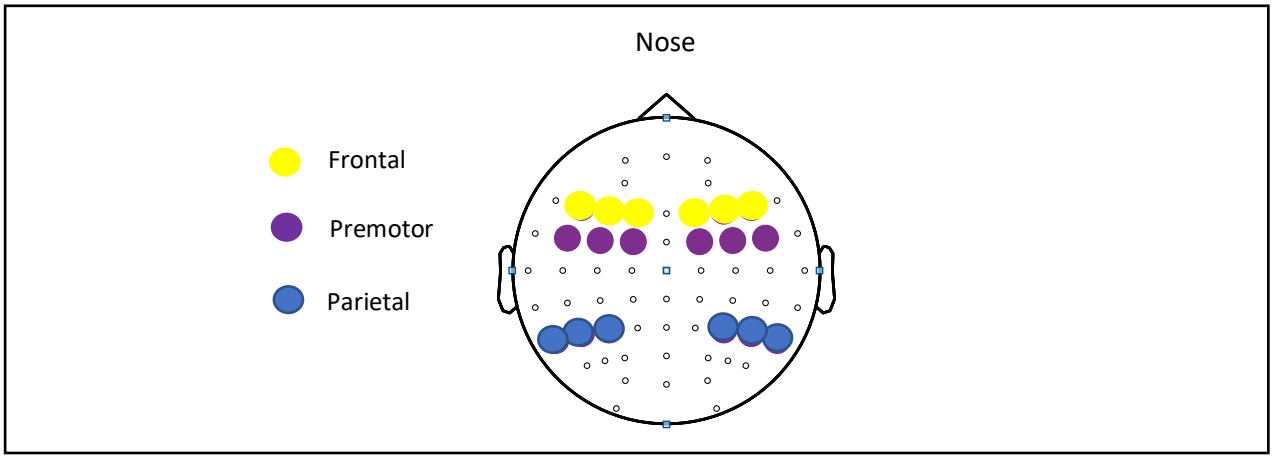

Figure 2: Regions of Interest (ROIs); frontal left and right ROSs are in yellow. Premotor ROIs are in purple. Parietal ROIs are in blue.

Chapter IV: Results

Introduction

In fulfillment of the study's intent to contribute to the limited body of knowledge on the effects of healthy aging on neural recruitment strategies supportive of every-day tool use; EEG data from individuals between the ages of 18-35(YG) and 60-85(OG) were collected during a visual choice-discrimination task. To examine the differences as compared to each other, EEG activity over bilateral premotor, and parietal regions of interest (Figure 2) in response to ideal (C1) and plausible (C2) tool-use scenarios is reported. Information from two latency windows is provided. The early latency window (L1) was between 100-250ms post-stimulus onset with the late latency window (L2) between 350-500ms post-stimulus onset. L1 includes sensory based stimulus processing and L2 incorporates the cognitive aspects of stimulus evaluation, understanding, and planning. YG and OG preformed comparatively in regards to correctly identifying the stimuli having 87.7% and 86.1% overall-correct, respectively. The response time was slower for OG (2207ms) than for the YG (1692ms). Percent-correct scores and reaction times are reported in Table 2. Significant differences, as determined by a corrected p-value (q) of .0143, were found in each of the regions of interest for at least one of the conditions (C1 or C2) are reported in Table 3.

	Responses	
	Younger	Older
Response Time (ms)	1692 (±608)	2207 (±658)
% Correct: Overall	87.7% (±3.2)	86.1% (±2.7)
% Correct: C1	89.1% (±1.2)	86.9% (±1.6)
% Correct: C2	86.3% (±2.4)	85.3% (±2.2)

Table 2: Average response time and percentage of correctly identified stimuli types are reported (± sd).

Frontal

Differences between the groups in both hemispheres of the frontal lobe for both conditions are in part demonstrated by the differences seen in the activity recorded by EEG during this choice-discrimination task. Significant differences in the activity of YG and OG were found in both latency windows in both conditions (Table 3). For C1, significant differences were found in the left ROI ($p = .01$, $q = .0221$) during the first latency window (L1). Here, OG showed reduced activity and was slower to reach maximum activity. The second latency window (L2) produced significant differences in both the left and right ROIs ($p = .0069$, $q = .0077$; $p < .001$, $q = .0014$). In the left, OG had less enhanced negative activity and a higher positive activity than YG. OG was slower to return to baseline than YG. In the right ROI during L2, OG was more active than YG (Figure 3). C2 produced significant differences between YG and OG in both hemispheres (Figure 4). During L1, the left ROI was significantly different between the groups ($p = .0119$, $q = .0313$). Here, OG had reduced activity overall. L2 only produced significant differences the right ROI ($p = .0091$, $q = .0138$). Here, OG has more activity than YG (Figure 4). Overall, frontal lobe ERPs indicate slower, more difficult processing in OG.

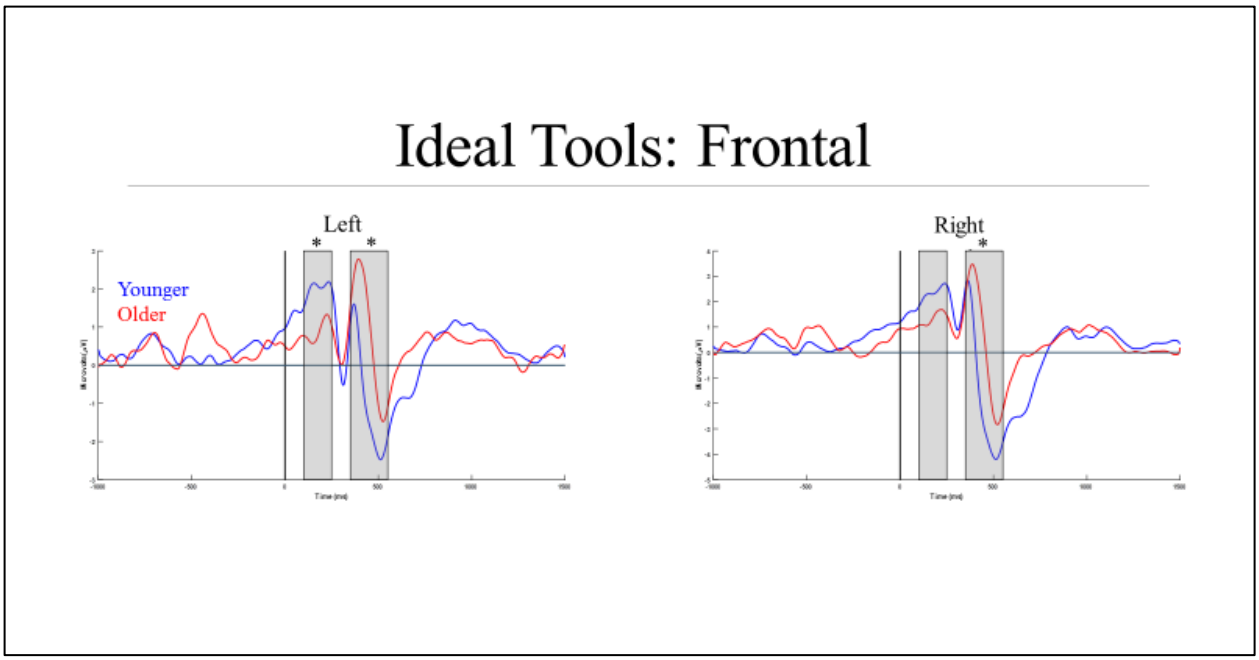

*Figure 3: ERPs generated by YG (blue) and OG (red) during C1 in the left (left) and right (right) ROIs of the frontal lobe. * indicates significant differences in activity.*

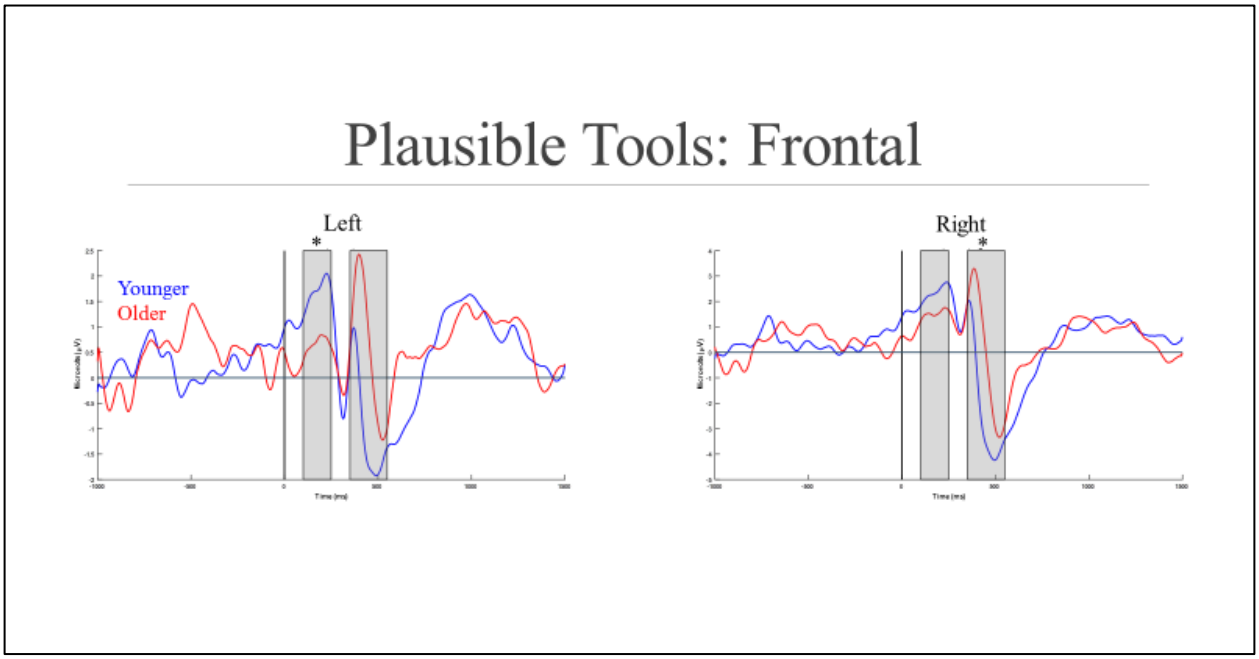

*Figure 4: ERPs generated by YG (blue) and OG (red) during C2 in the left (left) and right (right) ROIs of the frontal lobe. * indicates significant differences in activity.*

Premotor

Differences in premotor activity were seen between the groups in both conditions during both latency windows (Table 3). C1 produced differences in L1 in the left hemisphere (p = .0007, q = .0022). In the left and right hemisphere during L1, OG had reduced activity compared to YG. L2 produced differences in both the left and right hemispheres (p = .00029, q = .0007); p = .0003, q = .0007). During L2 in the left hemisphere, YG showed less activity overall compared to OG. This was also true in the right hemisphere (Figure 5). C2 produced differences in both latency windows (Table 3). In L1, differences were only significant in the left ROI (p = .0143, q = .0313). Here, OG showed reduced activity compared to YG. There were significant differences in the left and right hemispheres during L2 (p = .00069, q = .0022; p = .0019, q = .0039). In the left hemisphere during L2, OG had more activity than YG. Again, this was seen in the right ROI (Figure 6).

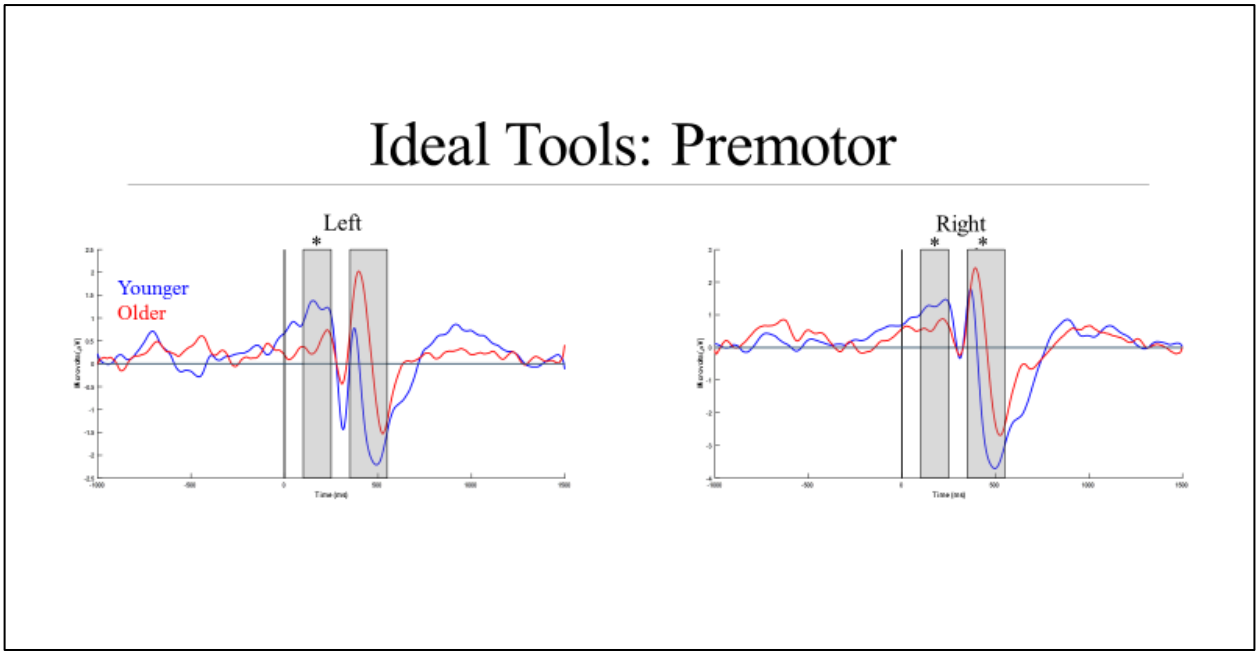

*Figure 5: ERPs generated by YG (blue) and OG (red) during C1 in the left (left) and right (right) ROIs of the premotor cortices. * indicates significant differences in activity.*

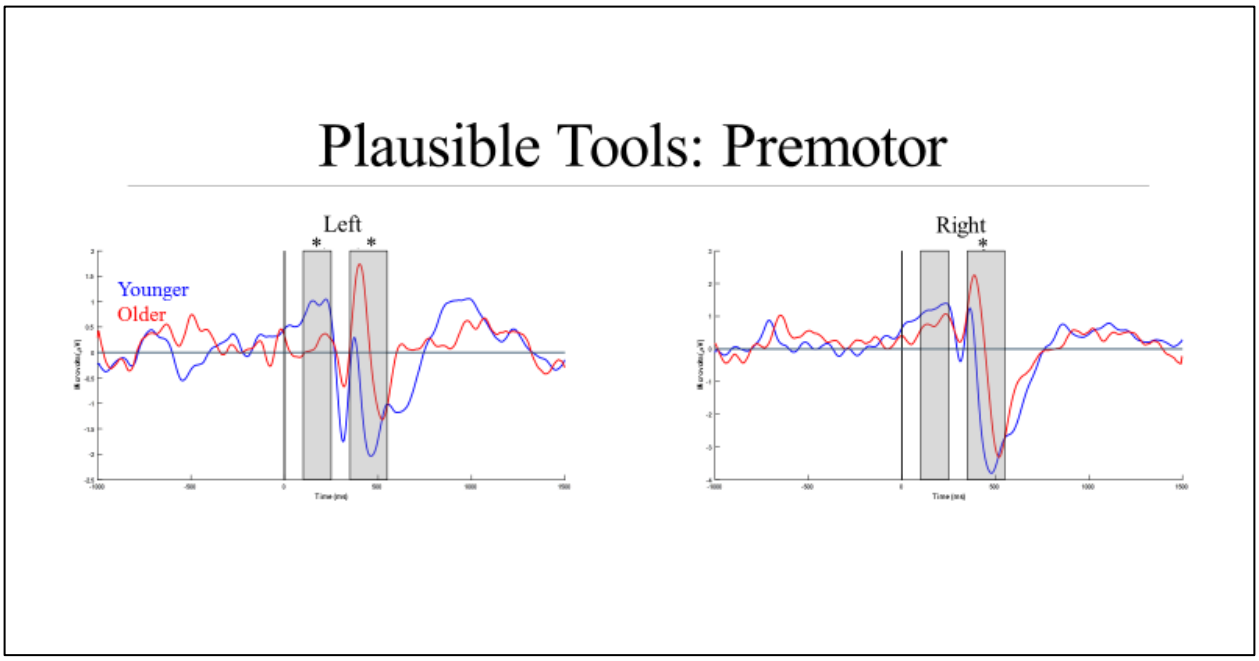

*Figure 6: ERPs generated by YG (blue) and OG (red) during C2 in the left (left) and right (right) ROIs of the premotor cortices. * indicates significant differences in activity.*

Parietal

In the parietal lobe, we observed significant differences in both latency windows and both conditions (Table 3). C1 produced differences in L1 only in the right hemisphere ($p = .0001$, $q = .0007$). In the right ROI, OG had less activity than YG. During L2, the left and right hemispheres were both significantly different when YG and OG were compared ($p = .0049$, $q = .0061$; $p = .0001$, $q = .0007$). In both the left and right hemispheres, there was less activity in OG compared to YG. This was also true for the right hemisphere (Figure 7). In C2, YG and OG were significantly different during L1 and L2 but only in the right hemisphere. Here, OG was less active than YG for both latency windows (Figure 8).

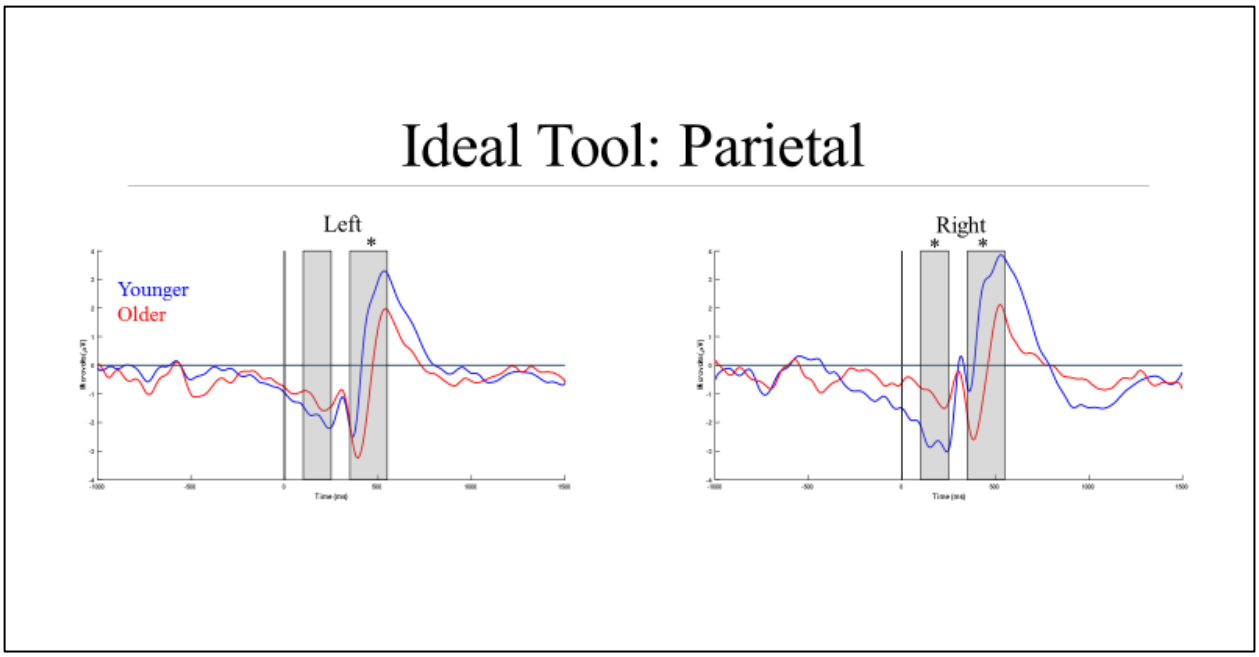

*Figure 7: ERPs generated by YG (blue) and OG (red) during C2 in the left (left) and right (right) ROIs of the parietal lobe. * indicates significant differences in activity.*

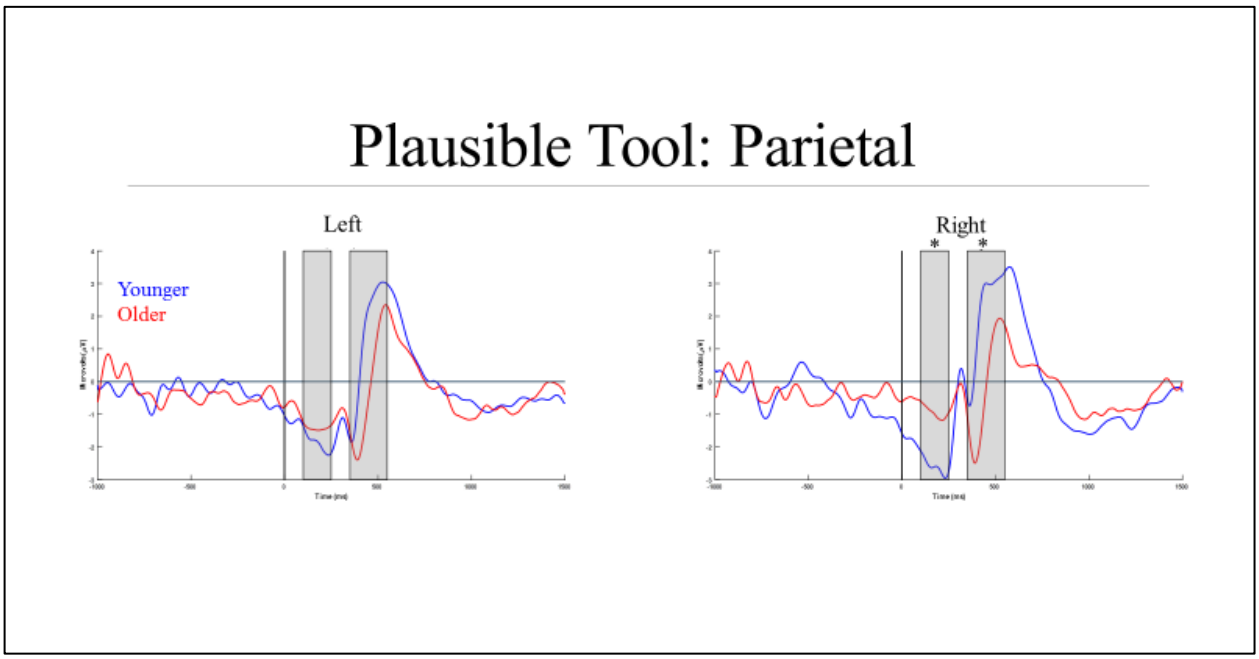

*Figure 8: ERPs generated by YG (blue) and OG (red) during C2 in the left (left) and right (right) ROIs of the parietal lobe. * indicates significant differences in activity.*

Summary

Overall, YG and OG had different approaches for evaluating ideal and plausible tools. C1 produced differences in the earlier processing stages in the left frontal, left premotor, and right parietal ROIs. In the same latency window, C2 produced differences in the same ROIs. During the later processing stages, C1 produced significant differences in all ROIs. C2 produced fewer differences in the same time window: the right frontal, both premotor, and right parietal ROIs. Differences in right frontal ROI only appeared in L2 but for both conditions. The left frontal ROI was significantly different during L1 and L2 in C1 but only L2 was significantly different in C2. The left premotor ROI was significantly different in L1 and L2 for both conditions. Right premotor differences were seen in both conditions but only in L2. The left parietal ROI was only different in L2 of C1. The right parietal, however, was different in both conditions and latency windows. These results were consistent with the literature in that HAROLD, PASA, and amplitude and latency shapes indicative of increased difficulty were present in older individuals. Further, OG performed similarly to YG. This implies that these changes in activation patterns are compensatory. These differences are outlined in Table 3.

Ideal			
100-250ms Post-stimulus Onset			
ROI	p	t	q
FL*	0.01	2.9879	0.0221
FR	0.0761	2.0754	-
PML*	7.00E10-04	3.6959	0.0022
PMR	0.1495	1.6527	-
PL	0.1265	-1.6437	-
PR*	1.00E-04	-4.3675	0.0007
350-550s Post-stimulus Onset			
ROI	p	t	q
FL*	0.0069	-2.9588	0.0077
FR*	9.00E-04	-4.7377	0.0014
PML*	3.00E-04	-4.3769	0.0007
PMR*	3.00E-04	-5.4500	0.0007
PL*	0.0049	3.2509	0.0061
PR*	1.00E-04	5.3469	0.0007

Plausible			
100-250ms Post-stimulus Onset			
ROI	p	t	q
FL*	0.0119	2.635	0.0313
FR	0.0693	2.0235	-
PML*	0.0143	2.8624	0.0313
PMR	0.1489	1.6145	-
PL	0.0943	-1.7512	-
PR*	0.0021	-3.4843	0.0138
350-550ms Post-stimulus Onset			
ROI	p	t	q
FL	0.0719	-1.943	-
FR*	0.0091	-3.0460	0.0138
PML*	7.00E-04	-4.3766	0.0022
PMR*	0.0019	-3.6285	0.0039
PL	0.0679	2.1319	-
PR*	5.00E-04	4.0819	0.0022

*Table 3: Original and corrected p-values for all ROIs separated by ideal (C1) and plausible (C2) conditions (left and right), latency(L1, top; L2, bottom), and ROI. FL = Frontal, left; FR = Frontal, right; PML = Premotor, left; PMR = Premotor, right; PL = Parietal, left PR =Parietal, right. * indicates significant differences in activity.*

Chapter V: Discussion

Introduction

In the literature, a general pattern of age-related changes in episodic memory, working memory, and executive functions have been thought to start in early adulthood (Salthouse, 2010). Age-related declines are generally thought to be related to morphological and neurophysiological changes in the brain. Currently, how some healthy older individuals are able to maintain the previously mentioned abilities while others cannot is unclear. This study aimed to better understand the cortical dynamics that support these abilities in healthy individuals throughout the lifespan. To achieve this, neural responses of 60-85 year-old participants to 18-35 year-old participants in "ideal" (C1) and "plausible" (C2) tool-use scenarios. More specifically, neural responses during early (L1; 100-250ms post-stimulus onset) and late (L2; 350-550ms post-stimulus onset) latency windows over bilateral frontal, premotor, and parietal regions of interest (Figure 2). L1 was included to evaluate the sensory-based processes while L2 was included to evaluate the cognitive aspects of the task. The regions of interest reported on were chosen because they have all been previously implicated in praxis-relevant action and understanding. Significant differences are summarized in Table 3. A better understanding of the neurophysiological differences between these healthy older and younger adults in successful tool-use and evaluation could be helpful in creating more personalized and effective rehabilitation programs for clinical populations as well as otherwise healthy older adults presenting performance deficits.

Ideal Tools

In C1, the left frontal ROI (FL) was significantly different in L1 and L2. In L1, OG had less activity than YG and seemed to reach peak activity slower. This is consistent with the idea that older adults have lower and slower ERPs and are less efficient at extracting and understanding stimulus information used to prepare a response. The reduction early activity has seen to be sensitive to correctly guessing where a stimulus will appear on the screen (based on a pervious stimulus) with correct guesses resulting in a greater amplitude (Mangun and Hilyard, 1991). However, location is not necessarily the only thing that impacts this activity as introducing a neutral pre-stimulus cue negates these effects (Luck et al., 1994). Meaning this difference could be because of the "cost" of attention that OG may have had less of initially when compared to YG (Luck, Woodman, and Vogel, 2000). Or, that YG was better able to match the stimulus with the description before. Differences in the right parietal ROI (PR) and left premotor ROIs were also seen during L1. According to HAROLD, older individuals often employ activation patterns that are described as a reduced activity in the primary region of one hemisphere and increased activation in the same area of the opposite hemisphere, reminiscent of a mirror-image (Cabeza, 2002). Because tool-related responses seen in PML and left posterior parietal cortices have been implicated in motor imagery and control (Grady et al., 1994; Jeannerod et al., 1995; Nyberg et al., 1996; Binkofski et al., 1999), differences in these area may represent differences in the ability of these groups to access stored information about object use-associated motor patterns (Martin and Chao, 2001). OG reached a peak in activity before YG in PR indicating OG attempted to process that information before YG needed to or because OG has adapted in such a way that requires the use information sooner instead of relying more on the left parietal ROI (PL) like YG. Differences in L1 ERP components of PR may be

attributed to the "cost" of guessing incorrectly and then having to re-evaluate the stimulus. It is not surprising that OG spent more time in this component but doing so sooner than YG did implies that healthy older brains adapt to allocate more time to the "where" and "how" of a tool. OG not activating their right frontal ROI (FR) differently than YG may just have been because the stimulus was obvious enough to process without needing the extra recruitment that this typically left-lateralized.

All regions of interest were different in L2. In FL during L2, latencies of the first and second negative peaks are essentially the same for YG and OG in both hemispheres. Activity, however, is larger for YG compared to OG in the left hemisphere and essentially the same for the for OG and YG in the right hemisphere. The negative activity is correlated with inhibition ability and could mean that YG had an easier time using the FL to inhibit incorrect button-presses or the were better able to disregarding irrelevant stimulus information when categorizing the stimulus compared to YG (Bruin and Wijers, 2002). Past research has focused on this negative activity as a mismatch detector and has recently been used in the study of language in addition to reflecting executive cognitive control functions (Folstein and Van Petten, 2008; Schmitt, Münte, and Kutas, 2000). This introduces the idea that YG was better able to decide if the tool matched the given scenario based on the text prompt (Patel and Azzam, 2005). OG showing less activity in FL but similar activity in FR (compared to YG) while maintaining this activity longer is consistent with the idea that areas under-activated in successful older individuals can be compensated for by recruiting the same area in the opposite hemisphere. OG maintains this activity longer which indicates that more time was spent in this component. That could be to compensate for a decrease in processing speed and efficiency as well as confirming that healthy older adults do depend more on anterior brain regions instead of posterior regions for longer

amounts of time (Davis et al., 2008). The left and right premotor ROIs (PML, PMR) had similar activity to FL and FR. Indicating, again, that these areas change, at least functionally, together to help support cognitive function in everyday tool-use. During L2 in the PR and PL ROIs, activity was higher in YG than in OG. This reflects differences in general neural processing that occur when visual (or other) sensory input is compared to internal representation from memory or landscape context (Freunberger, Klimiesch, Doppelmayr, and Holler, 2007; Evans and Federmeier, 2007). In general, the activity differences indicate that YG more efficiently extract information from the stimulus and more quickly apply it (Bekker et al., 2005). In FR, similarities in ERP shape between groups implies that OG relied on both hemispheres during the task while still requiring more processing time. This further highlights YGs ability to process information faster and more efficient attention and memory functions (Kropotov et al., 2016). These results also carried over into PML and PMR. In PL and PR, L2 has been seen to correlate with recognition of stimuli (Fischer et al., 1983). In both PL and PR, YGs activity points to YG being able to establish recognition sooner than OG. YG returinging to baseline sooner than OG indicates YG is better able to prepare a motor response (Dirnberger, Lang, and Lindinger, 2010).

Plausible Tools

C2 produced significant differences during both L1 and L2. During L1, significant differences were found in FL, PML, and PR. These were the same areas that were different during L1 for the ideal tool condition. In FL during L1 OG was less active than YG. The ERP shape indicates OG began trying to extract and understand stimulus information relevant to preparing a correct response sooner than YG. This would allow OG more time to identify stimulus relevant information. The reduced activity could have been due to initial attention capacity was less active for OG. The ERP shape implies that OG compensated for reduced

efficiency by allocating more time to prepare a response. Differences in activity during L1 of PR may be attributed to the "cost" of guessing incorrectly and then having to re-evaluate the stimulus. This indicates that OG attempted to process stimulus relevant information before YG or that OG was preparing to re-evaluate the stimulus sooner than YG. Accessing this information sooner and employing both hemispheres, instead of relying on the left parietal ROI (PL) like YG, reinforces HAROLD and our hypothesis regarding bilateral activity in older individuals.

L2 produced differences in FR, PML, PMR, and PR. In FR, OG was more active than YG but not in FL. The differences in FR and lack thereof in FL could mean that OG was maximally activated in FL trying to employ activation strategies typical of a younger brain but needed to compensate for their reduced capacity in FL by recruiting FR. More activity in FR indicates the ability to extract information from the stimulus and more quickly apply it (Bekker et al., 2005). These differences indicate YGs ability to process information faster, and more efficient attention and memory functions (Kropotov et al., 2016). The activity here implies that OG spent more time evaluating the stimulus but still less effectively recognized or paired it to the text prompt. OG has less area under their latte negative component and reaches it later than YG. Overall, activity here implies that YG did not work as hard in this ROI to recognize stimuli and have more resources available to prepare a response. Both premotor ROIs were significantly different during L2 for C2. The early negative activity was exaggerated in YG with similar peak latencies in PML and PMR. The activity patterns here imply that OG had a harder time inhibiting incorrect button presses as the primary motor cortex is not far from this ROI. These qualities point to OG having to rely on the right hemisphere to make up for deficits in PML. They could also mean that OG had a harder time disregarding irrelevant stimulus information during stimulus categorization or deciding if there was a mismatch. The positive activity in PML and

PMR are higher for OG compared to YG. Both regions being significantly different in this condition compared to C1 implies that more complex stimuli require OG to allocate more time and resources to evaluation and less on the actual motor response at least in PML. The shift back to baseline is more similar in shape to YG in PMR which implies that OG was less efficient in using PML but was able to compensate by activating PMR differently. PR activity has been seen to index the ability to recognize stimuli as well as better prepare a motor response (Dirnberger, Lang, and Lindinger, 2010). Dien demonstrated this negative activity increases in negativity with the presentation of incongruent stimuli while increases in positivity were seen for congruent stimuli. They suggest that this dynamic represents integration into a sequential representation or updating of general sequential expectancies (Dien, Michelson, and Franklin, 2010). It is further suggested by Dien et al. that the negative activity appears to be semantic in nature and that suggest that the shift to the positivity reflects a general sequential expectancy system. L2 is commonly studied in regards to language and is generally thought to be evoked when syntax errors are made or more complicated stimuli are present- as demonstrated by an increase in activity. Reduced activity here could indicate that OG was challenged in recognizing that the tool was not ideal. This could have also been caused by C2 being a complicated stimulus compared to C1 (Kaan and Swaab, 2003). A better understanding of the complex relationship between these components potentially explains some aspects of cognitive motor control over the lifespan.

Conclusions

As the percentage of the population over the age of 65 continues to rise, so does the need for effective training programs designed to recognize and slow age-related loss of praxis knowledge and improve cognitive motor function. Because goal-directed associative memory retrieval is thought to depend on top-down signals from the anterior prefrontal cortex and medial

temporal lobes (Ranganath, Cohen, Dam, and D'Esposito, 2004) with inputs from a network of primarily left-lateralized regions that process online visuo-motor transformations for grasping objects (posterior parietal cortex) and the motor commands associated with tool use (inferior parietal lobule) (e.g., Culham et al., 2003, Beauchamp and Martin, 2007, Johnson-Frey, 2004), the present study investigated group differences and similarities in the activation patterns of bilateral frontal, premotor, and parietal regions of interest. These comparisons were made over early and late latency windows to include the evaluation of different aspects of perception and planning.

We hypothesized that OG would show increased bilateral activity, specifically HAROLD, compared to the younger population in ideal and plausible tool-use scenarios. This was evident in frontal, and premotor ROIs. Second, we expected a shift from recruiting posterior brain regions to an anterior focus (PASA) in OG would be seen for C1 and C2 compared to YG. This was confirmed by the activity patterns seen in the parietal lobe- where YG was more active. Lastly, differences between the groups' amplitudes within both latency windows indicative of greater difficulty in OG compared to YG was expected and seen in the shapes of the ERPs.

In FL, YG was more active in L1while OG was more active in L2. On the other side, FR showed greater activity for OG in L2 that was significantly different from YG. As previously mentioned, L1 is sensory-perception based and L2 involves more cognitive processes. During C1-L1, YG was more active which implies that object perception was more difficult for OG but not so much so that they had to rely on bilateral activation. During C1-L2, FL was the area expected to be used by healthy younger adults during this task. So, seeing OG being more active in this area during L2 makes sense. OG activating FR more in L2 is in line with confirms the idea of HAROLD. Looking at the next condition, C2-L1 in the frontal ROIs, the results were

similar and imply the same. During C2-L2, OG and YG were not significantly different in FL-L2. This could be because this condition was complex enough to make YG work a little harder in FL-L2, negating the differences in this ROI. OG still activated more in FR indicating that they were still relying on bilateral activation of the frontal ROIs to effectively evaluate the object and scenario presented in C2.

In the premotor cortices, bilateral activation was seen in OG during L1 but not L2. During C2, OG only bilaterally activated during L2. Activation pattern differences in L1 here could be explained by "ideal" tools elicited more social constructs indicative of movement intention. Because activity in this time window have been correlated with social constructs and movement intention, it is possible that the that the "ideal" tool condition elicited bilateral activity in OG during L1 because of the built-in social constructs that come with "ideal" tools; whereas, the "plausible" tool did not possess these qualities and thus did not elicit bilateral activation during L1. FL being the same while FR was different in C1-L2 implies that OG still activated differently in the later cog stages than YG did. C2-L1 patterns imply that the stimulus information was harder for OG but not enough to activate bilaterally. Bilateral activation in C2-L2 implies that OG relied on both hemispheres during the later processing stages to decide if the plausible tool was in fact plausible or if it was in one of the other possible stimulus categories: incorrect manipulation, incorrect context, hand, or tool.

In the parietal ROIs, regardless of condition, YG was more actively engaging their right hemisphere throughout both latency windows. However, YG and OG were similar in their use of the PL with the exception of L2 during C1. This suggests a heavier reliance on anterior brain regions for healthy older individuals compared to healthy younger individuals use of the parietal lobe during action encoding and preparation. The differences between these two populations in

C1 and C2 confirmed that healthy older adults employ bilateral and anterior activation patterns seen in the literature. Because OG had similar performance to YG, these activation patterns seem to be compensating for the increased difficulty and inefficiency of praxis related areas and processes that accompany old age. The altered activations in frontal, premotor, and parietal regions identified here could be useful in creating more personalized and effective rehabilitation programs. Such as, programs geared towards maintaining the function of the parietal cortices in healthy older individuals or individuals with cerebrovascular accidents. Further, these findings support employing targeted, preventative strategies aimed at improving the function of the frontal and premotor cortices in the growing population of otherwise healthy older adults to sustain functional independence.

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Appendix A: Institutional Review Board Approval

EAST CAROLINA UNIVERSITY
University & Medical Center Institutional Review Board
4N-64 Brody Medical Sciences Building· Mail Stop 682
600 Moye Boulevard · Greenville, NC 27834
Office **252-744-2914** · Fax **252-744-2284** ·
www.ecu.edu/ORIC/irb

Notification of Continuing Review Approval: Expedited

From: Biomedical IRB
To: Chris Mizelle
CC:

Date: 10/1/2018
Re: CR00007228
UMCIRB 15-002065
Aging and Cognitive Motor Control

The continuing review of your expedited study was approved. Approval of the study and any consent form(s) is for the period of 10/1/2018 to 9/30/2019. This research study is eligible for review under expedited category #4. The Chairperson (or designee) deemed this study no more than minimal risk.

Changes to this approved research may not be initiated without UMCIRB review except when necessary to eliminate an apparent immediate hazard to the participant. All unanticipated problems involving risks to participants and others must be promptly reported to the UMCIRB. The investigator must submit a continuing review/closure application to the UMCIRB prior to the date of study expiration. The Investigator must adhere to all reporting requirements for this study.

Approved consent documents with the IRB approval date stamped on the document should be used to consent participants (consent documents with the IRB approval date stamp are found under the Documents tab in the study workspace).

The approval includes the following items:

Document	Description
Mizelle.Aging-EEG.Consent.11122015.doc(0.01)	Consent Forms
Mizelle-Aging-EEG-Protocol.v1.docx(0.01)	Study Protocol or Grant Application
Research.Study.Flier.doc(0.02)	Recruitment Documents/Scripts

The Chairperson (or designee) does not have a potential for conflict of interest on this study.

Appendix B: Approved Consent Form

East Carolina University

Informed Consent to Participate in Research

Information to consider before taking part in research that has no more than minimal risk.

Title of Research Study: A Research Study of the Effects of Aging on Cognitive Motor Control

Principal Investigator: J.C. (Chris) Mizelle, Ph.D.
Institution, Department or Division: East Carolina University / Department of Kinesiology
Address: 170B Minges Coliseum
Telephone #: 252-328-9271

Researchers at East Carolina University (ECU) study issues related to society, health problems, environmental problems, behavior problems and the human condition. To do this, we need the help of volunteers who are willing to take part in research.

Why am I being invited to take part in this research?
General reductions in associative and relational knowledge have been well documented in healthy older adults. However, these deficits have yet to be fully characterized in processes related to daily activities, such as tool use. It is unclear whether age-related performance deficits arise from neuroanatomical alterations, or from more subtle changes in the functional properties of regions and networks for (normally) routine processing tasks. It is also unclear whether context- or action-related processes are more affected by the aging process. The proposed research seeks to address these questions by using electroencephalography (EEG) to evaluate the brain activity that supports cognitive motor processes in healthy young and older adults.

You are being invited to take part in this research because you are a healthy volunteer who meets our inclusion and exclusion criteria. The decision to take part in this research is yours to make. By doing this research, we hope to learn how the brain processes tool use in daily tasks, and how aging might affect these processes.

If you volunteer to take part in this research, you will be one of about 50 people to do so.

Are there reasons I should not take part in this research?
You should not volunteer for this study if you are not between the ages of 18-35 or 60-84, if you do not have normal or corrected-to-normal vision, if you are not right handed, or if you have any previous history of serious neurological or upper extremity neuromuscular illness or injury.

What other choices do I have if I do not take part in this research?
You can choose not to participate. Your participation is strictly voluntary.

Where is the research going to take place and how long will it last?
The research will be conducted at East Carolina University, in the laboratory of Dr. Mizelle (170 Minges Coliseum). You will need to come to 170A Minges Coliseum one time during the study. The total amount of time you will be asked to volunteer for this study is 2 ½ hours over one day.

What will I be asked to do?

You will be asked to do the following: participate in a research study designed to help us understand how the brain processes tool-related information in daily tasks. Please read through the section related to your participation below. Please ask any questions you may have about your participation.

If you decide to participate in this study, you will come to the Sensorimotor Control Lab (room 170A in Minges Coliseum, East Carolina University) for a single visit lasting approximately 2 ½ hours. You will be asked to look at a set of images and videos of tools being used in everyday activities while brain signals are being recorded with electroencephalography (EEG). Your task will be to determine if the tools are being used in ways that are correct, incorrect, or unusual, and to press a button based on your response. For EEG recording, you will sit in a chair with arms placed on the armrests in a dimly lit room. A special cap with many sensors will be fitted to your head and connected to a computer system that measures brain activity. Once the cap and sensors are properly set and prepared, you will begin looking at images and videos. The EEG session will last less than 1 hour. After the EEG session, a digital instrument will be used to record the sensor locations on your head. This will conclude the experiment.

What might I experience if I take part in the research?
EEG is a non-invasive test. However, participants may experience some discomforts, which are common to the EEG procedures as a result of taking part in this study. There may be mild discomfort and adhesive residue apparent upon the removal of certain EEG sensors. There may be temporary alteration of hairstyle after removal of the EEG cap and some subjects may experience minimal hair loss. Impression marks from the EEG cap and sensors will also be present after the research study, but will resolve shortly after the research study is completed.

Will I be paid for taking part in this research?
We will be able to pay you for the time you volunteer while being in this study. At the end of your participation, you will receive a Target gift card valued at $15.

Will it cost me to take part in this research?
It will not cost you any money to be part of the research

Who will know that I took part in this research and learn personal information about me?
ECU and the people and organizations listed below may know that you took part in this research and may see information about you that is normally kept private. With your permission, these people may use your private information to do this research:

- Any agency of the federal, state, or local government that regulates human research. This includes the Department of Health and Human Services (DHHS), the North Carolina Department of Health, and the Office for Human Research Protections.
- The University & Medical Center Institutional Review Board (UMCIRB) and its staff have responsibility for overseeing your welfare during this research and may need to see research records that identify you.

How will you keep the information you collect about me secure? How long will you keep it?
All personally identifiable information, such as this form, will be kept in a locked file cabinet within Dr. Mizelle's office, thus providing two levels of security. You will be assigned a participant number that will be used to track performance, and a hard copy of the key to breaking the subject codes and related identifiers will be held under lock and key Dr. Mizelle's secured office space. Your name and participant number will not be identified in any subsequent report or publication. All electronic data (EEG) will be fully de-identified, and will be kept for storage on an encripted hard drive, also inside Dr. Mizelle's locked office. All research records and/or identifiers will be securely maintained for 5 years past the completion of the study, and will then be securely destroyed. It is also possible that your de-identified data may be used in future research without anyone knowing it is information from you.

What if I decide I don't want to continue in this research?
You can stop at any time after it has already started. There will be no consequences if you stop and you will not be criticized. You will not lose any benefits that you normally receive.

Who should I contact if I have questions?
The people conducting this study will be able to answer any questions concerning this research, now or in the future. You may contact the Principal Investigator at 252-328-9271 (days, between 9:00 am and 5:00 pm).

If you have questions about your rights as someone taking part in research, you may call the Office of Research Integrity & Compliance (ORIC) at phone number 252-744-2914 (days, 8:00 am-5:00 pm). If you would like to report a complaint or concern about this research study, you may call the Director of the ORIC, at 252-744-1971.

I have decided I want to take part in this research. What should I do now?
The person obtaining informed consent will ask you to read the following and if you agree, you should sign this form:

- I have read (or had read to me) all of the above information.
- I have had an opportunity to ask questions about things in this research I did not understand and have received satisfactory answers.
- I know that I can stop taking part in this study at any time.
- By signing this informed consent form, I am not giving up any of my rights.
- I have been given a copy of this consent document, and it is mine to keep.

Participant's Name (PRINT)	**Signature**	**Date**

Person Obtaining Informed Consent: I have conducted the initial informed consent process. I have orally reviewed the contents of the consent document with the person who has signed above, and answered all of the person's questions about the research.

Person Obtaining Consent (PRINT)	**Signature**	**Date**