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Effects of Chronic Opioid Use on Short-Term Working Memory and Executive Functions

by

Sydni L. Arnold

A thesis

submitted in partial fulfillment

of the requirements for the degree of

Master of Science in Speech-Language Pathology

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Committee Approval

To the Graduate Faculty:

The members of the committee appointed to examine the thesis of Sydni Arnold find it satisfactory and recommend that it be accepted.

Dr. Nicholas Altieri,
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June 10, 2014

Nicholas Altieri, PhD
Mail Stop 8116
CSED
Pocatello, ID 83209

RE: Your application dated 6/10/2014 regarding study number 4090: Impact of Chronic Opioid Medication Use on Neuro-Cognitive and Language Functions (Mountain West Clinical Translational Research)

Dear Dr. Altieri:

Thank you for your response to requests from a prior review of your application for the new study listed above. Your study is eligible for expedited review under FDA and DHHS (OHRP) designation.

This is to confirm that your application is now fully approved. The protocol is approved through 6/10/2015.

You are granted permission to conduct your study as most recently described effective immediately. The study is subject to continuing review on or before 6/10/2015, unless closed before that date.

Please note that any changes to the study as approved must be promptly reported and approved. Some changes may be approved by expedited review; others require full board review. Contact Thomas Bailey (208-282-2179; fax 208-282-4723; email: humsubj@isu.edu) if you have any questions or require further information.

Sincerely,

Ralph Baergen, PhD, MPH, CIP
Human Subjects Chair

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Abstract

While experts are aware of the addictive properties of opioid analgesics, there is a lack of research of the long term side effects of prolonged opioid use on memory, language, and cognition. Because many individuals use opioids for temporary pain relief as well as long term pain management, answering the question, "What are the effects of chronic use of opioids on memory and executive function?" will provide beneficial information for individuals who use opioid analgesics to treat chronic pain, such as cancer pain, as well as pain management experts and insurance companies. It is hypothesized that long term use of opioids will cause impairments in memory, particularly short-term memory, and executive function as measured by poorer performance on tests of inhibition, attention, and cued recognition. It is expected that the proposed research will provide new data regarding the effects of opioid use on sensory and cognitive abilities.

Effects of Chronic Opioid Use on Short-Term Working Memory and Executive Functions

Opioid treatment for pain management has become increasingly common, and as a result, adverse effects related to chronic use and dependency has been investigated (e.g., Meera, 2011). Additionally, not only have several studies revealed that opioid analgesic prescriptions have increased, but there were also more deaths from overdoses of prescription analgesics than from heroin or cocaine (Stovel, Knopf, Enos, Merrill, Devaux, & Lewis, 2007). For example, between 1999 and 2002, there was an increase of 91.2 percent in deaths due to opioid poisoning (Stovel et al., 2007).

In spite of a considerable body of research on the addictive properties of opioid pain medications, research regarding the cognitive side effects of opioid use is comparatively limited. Specifically, the extent to which attention, short-term and working memory, and organizational abilities are adversely affected by chronic opioid use remains unknown. Collectively, these abilities are often referred to as "Executive Functions" (Roth, Isquith, & Gioia 2005). Previous studies have, for example, reported significant deficits in recognizing the emotional state of others in chronic opioid users (McDonald, Darke, & Torok, 2012; Rapeli et al., 2006). Additionally, a related study focused on the relationship between opioid use and cognitive impairment after hip fracture repair (Sieber, Hochang, & Gottschalk, 2011). The authors sought to determine if opioid administration was significant factor in post-surgical delirium, which is a major problem in otherwise cognitively healthy elderly adults. The observations failed to indicate a correlation between postoperative opioid use and incident delirium. Interestingly, this study indicates that short-term opioid administration is not responsible for delirium post-surgery; other factors, such as dementia, were more critical factors for confusion.

However, the long-term effects on cognition remain largely unknown. To investigate the long term effects of opioid use, Rapeli et al., (2006) sought to determine the extent to which cognitive deficits were presented in recently abstinent opioid users, and whether these cognitive deficits were temporary. The participants included 15 opioid dependent users that volunteered from Helsinki University Central Hospital drug detoxification unit and 15 controls. Independent variables of interest included duration of opioid use and withdrawal symptoms. Dependent variables included performance on cognitive tests, including assessments of working memory, episodic memory, executive function, and fluid intelligence. Cognitive testing was presented in an alternating fashion (difficult and easy, verbal and nonverbal, and memory and non-memory) and were completed randomly between five to 15 days from the last opioid dose. The Short Opiate Withdrawal Scale (SOWS) was used to measure withdrawal symptoms. Results indicated that early abstinent opioid dependent patients performed worse in areas of cognitive function such as working memory, executive function, and fluid intelligence. In addition, many domains of executive function were predictive of one another, and with the number of days of medication withdrawal. For example, working memory and fluid intelligence abilities both presented a strong correlation with number days of withdrawal.

Another study focused on the relationship between social perception and cognition and opioid users (McDonald, Darke, & Torok, 2012). The study carried out by McDonald et al. (2012) was designed for two reasons: First, the authors wanted to compare performance on social perception tasks among opioid maintenance patients

(MAIN), abstinent opioid users (ABST), and non-opioid users (CON). Secondly, they wanted to identify the extent to which deficits in social cognition can be accounted for by co-occurring cognitive deficits or risk factors for brain damage. Results indicated that poor cognitive function played a crucial factor on the performance on The Awareness of Social Inference Test (TASIT 1) and TASIT 2. The researchers also noted that these findings may be a result of brain injuries among the MAIN group members. Furthermore, poor performance on the TASIT 1 and 2 suggested that opioid users struggle to recognize the emotional state of others, including sarcasm, which may cause a disruption in communication. The results of this study suggest that social perception deficits may be a result of chronic opioid use. However, it is unknown whether the deficits in social cognition are strictly related to opioid use or whether other socioeconomic, environmental, or cognitive factors are at work.

Finally, previous studies have suggested that co-morbid conditions may also be a contributing factor of cognitive decline in patients prescribed opioid medications. One study discussed how other medications may impact opioid therapy (Smith & Bruckenthal, 2010). This is important to present in current research because polypharmacy may influence the increase or decrease of cognitive decline, if any, seen in patient's that demonstrate prolonged opioid dependency. Furthermore, this same study states that opioid use can highly impact the central nervous system (CNS) when patients have illnesses such as cerebrovascular disease, dementia, or brain injury (Smith & Bruckenthal, 2010). It is important to consider these co-morbid conditions when collecting data for research. Not only does opioid dependency highly impact the central nervous system, it may also have a negative impact on executive functions.

Opioid Medication Use and Executive Dysfunction

Executive functions, a subset of which is often referred to as *working memory,* are cognitive functions involved in the organization, manipulation, and storage of information. The frontal lobe functions of attempting to memorize the digits of a phone number and filtering out background noise when attending to a speaker are examples of the executive functions of working memory, attention, and inhibition respectively.

Components of Executive Function

Roth, Isquith, and Gioia (2005) identified nine major sub-components of executive function: plan, shift, initiation, emotional control, self-monitor, task-monitor, inhibition, attention, and working memory. *Plan* involves organizing anticipated future events, developing appropriate steps to meet goals in a systemic manner. *Shift* refers to being flexible in problem solving while moving freely from one aspect of a problem to another, when needed. *Initiation* is the ability to start a new task or activity. Appropriately managing emotional responses refers to *emotional control. Self-monitor* is the ability to keep track of the effect of own behavior on others, and attend to own behavior, in a social context. *Task-monitor* allows individuals to assess own performance during a task to ensure attainment of goals.

Inhibition involves the ability to stop an ongoing or dominant response and interference control (Vuontela et al., 2012). Cohen (1993) described neural inhibition into 4 categories: reciprocal, antagonistic, unidirectional, and lateral. Reciprocal inhibition occurs when the same system is involved in the initiation and termination of an activity. Antagonistic inhibition relates to incompatible responses in which the responses are controlled by differing structures. Unidirectional inhibition involves one subsystem (involving both cortical and subcortical structures) having an impact on another through direct pathways. Lateral inhibition occurs when adjacent neurons influences one another which results in an altered response (Riccio, Reynolds, Lowe, & Moore, 2002). *Attention* relates to the ability to focus on a relevant cue, task vigilance, and inhibiting responses to irrelevant stimuli (Vuontela et al., 2012; Riccio, Reynolds, Lowe, & Moore, 2002). Attention involves the interaction between cortical and subcortical structures along with pathways/projections between the basal ganglia, thalamus, and frontal lobes (Riccio, Reynolds, Lowe, & Moore, 2002).

Finally, *Working memory* consists of a set of cognitive functions that allow us to simultaneously manipulate and maintain information for short periods of time in an active state (McCabe, Robertson, & Smith 2005; Vuontela et al., 2012). Nelson Cowon, a well-known professor at the University of Missouri who specializes in working memory, provides an integrated model of working memory that represents working memory as a subset of representations held in long-term memory.

Variability in Executive Function Capabilities

Both clinical and "normal" individuals show considerable variability in their abilities to perform tasks that demand working memory or other executive functions. Performance on these tasks may be influenced by many cognitive and developmental factors. Additionally, previous studies have suggested that co-morbid conditions may also be a contributing factor of cognitive decline—notably in patients prescribed opioid medications (Smith & Bruckenthal, 2010) . One study in particular discussed how other medications may impact opioid therapy (Smith & Bruckenthal, 2010). This is important in current research because polypharmacy may influence cognitive decline observed in patients that have demonstrate prolonged opioid dependency. Furthermore, this same study states that opioid use can impact the central nervous system (CNS) when patients have illnesses such as cerebrovascular disease, dementia, or brain injury (Smith & Bruckenthal, 2010). It is important to consider these co-morbid conditions when collecting data for research.

When individuals have executive function and memory deficits, they may demonstrate signs of inattentiveness, poor time management, and reduced organizational skills**.** These deficits are often found in aging individuals, as found in a study by McCabe, Robertson, and Smith (2005). The purpose of their study was to determine if older adults (between the ages of 62 and 80) demonstrated significantly greater difficulty in using controlled attention in short-term memory when compared to younger adults (ages 18 to 29). All participants were shown a sequence of color-words and were asked to remember the color of each word. When the word RECALL appeared, they were asked to write down the first letter of each of the incongruent (e.g. the word “red” written in yellow font). Not only did the study conclude that older adults were more likely to make errors on a task requiring recall of the color-words from working memory, but they were also more susceptible to inference in working memory. The authors also reported that older adults struggle with effectively allocating attention to task demands. Specifically, the authors observed an increased error rate on incongruent color-word combinations in older adults Results also suggested that inhibitory efficiency decreased with memory load in older adults, and that working memory capacity is positively correlated with frontal-lobe functioning (McCabe, Robertson & Smith, 2005).

The following section will address a relationship that has been discovered in recent years—the association between chronic opioid use and deficits in one or more executive-function sub-components described above.

Working Memory Capacity

A study by Wenger, Negash, Petersen, and Petersen (2010) sought to compare the advantages of using a measure of capacity versus measures of mean accuracy and mean reaction time in differentiating individuals with mild cognitive impairment from those without. This study was done by gathering data from five groups of participants. The first group, called CA group, consisted of healthy undergraduate students. The second group, titled the MA group, included healthy middle aged adults between the ages of 25-65. The third group was called the HE-SB group and consisted of healthy elderly individuals. Group four consisted of 50 individuals that were diagnosed with a diagnosis of mild cognitive impairment and were referred to as the MCI group. Group five, called the MCI-C group, involved 50 aged-matched controls. After the background questionnaire was completed, a visual identification thresholds task, a naming time task, and FCSRT were administered. The visual identification threshold task and the naming time task provided measures that would be useful in distinguishing latency-based effects specific to memory processing from general age-related slowing.

The FCSRT required participants to find a target image located in a display involving three randomly selected non-target images on the basis of both a category cue and a related instance cue. The locations of the target image varied depending on the encoding trial. Each trial was initiated and terminated by the experimenter. After the entire list of target items had been presented, subjects were asked to verbally recall as many of the encoded items as possible. A cued recall trial was initiated after the item was correctly recalled. The cued recall trial began with the presentation of either one or two cues at the top of the screen. The cue(s) were available until the participant responded verbally. The RT for the trial was the time from onset of the retrieval cue(s) to the onset of the participant's vocal response.

The authors observed that adding an additional cue produced a reduction in capacity for participants in all five groups; however, the MCI group appeared to be more sensitive to the effect of carrying processing load, showing both negative and positive effects for increasing the number of cues. These findings demonstrated that measures of capacity revealed more changes with degeneration of hippocampal atrophy than measures of speed of processing. Because of the sensitivity of capacity, using these measures to assess cued-memory in opioid users will be beneficial for determining the long term effects of opioid use on individuals.

Methods

This thesis will apply behavioral and self-report standardized test subscales to a group of randomly sampled middle-aged opioid users to investigate the extent to which opioid medication use impairs the various domains of cognitive function. The following section will describe standard scales used for assessing executive functions in a self-report standardized assessment of executive function (BRIEF-A). The behavioral tests assessing recognition memory, attention, processing speed, and inhibition will be introduced subsequently to the BRIEF-A.

BRIEF-A: Executive Function Subscales and Measurement

As previously described, executive functions are cognitive "control processes" including: organization, direction, and organization of cognitive activities and emotional responses (see Roth et al., 2005). More specifically, executive function includes nine subscales: plan, shift, inhibition, initiation, emotional control, self-monitor, task-monitor, attention, and working memory. The subscales can be measured by self-report and the Behavior Rating Inventory of Executive Function-Adult Version (BRIEF-A). The nine subscales of the BRIEF-A are described in Table 1 below:

The BRIEF-A provides information on the patient's ability to perceive their own executive functioning. It provides 75 items that assesses the 9 subscales of executive functions while simultaneously assessing three validity scales: negativity, infrequency, and inconsistency.

Table 1: The Nine Subscales Presented in the Behavior Rating Inventory of Executive Function- Adult Version

Subscale	**Description**
Plan	Develop steps to accomplish goals in a systematic manner.
Shift	Easily transfer from one activity or problem to another
Inhibition	Control impulses.
Initiation	Begin task or activity.
Emotional Control	Regulate emotional responses properly.
Self- Monitor	Recognize effect of own behavior on others in social context.
Task- Monitor	Assess work and performance.
Attention	The ability to focus on the relevant portion of a task.
Working Memory	Retain information in order to complete task.

Behavioral Assessments

One major contribution of this study will be the administration of tests that assess processing speed and accuracy in addition to the self-report measures provided by the BRIEF-A. These measures have the potential to provide more fine-grained detail about underlying deficits in cognitive function, and in addition, may be correlated with BRIEF subscales. For example, processing speed decreases with aging is likely adversely affected by accompanying declines in executive function (McCabe, Robertson, & Smith, 2005). Measurements therefore need to assess how changes in processing speed, working memory, and attention co-vary with changes in executive function. For instance, research indicates that aging impacts cognitive skills across a variety of domains including abstract reasoning, conceptual problem solving, planning, mental tracking and manipulation that manifest as changes in processing speed and accuracy (Starns & Ratcliff, 2010; Roldan-Tapia, Garcia, Canovas, & Leon, 2012). Furthermore, several studies have associated aging to memory decline, particularly with associated memory, as well as changes in perceptual decision criteria that contribute to slower response times (RTs) (Ratcliff, McKoon, & Thapar, 2011; Ratcliff, Thapar, & McKoon, 2004).

Executive functions subcomponents, such as inhibition, will be measured by presentation of many tasks. Processing speed and inhibition will be measured using a Go-No-Go task in which participants will be presented stimuli that represent a “go” or “no go.” A Flanker/Arrow Task will be used to examine inhibition and attention. This task requires participants to determine if the arrow is congruent or incongruent corresponding arrows. A Cued Memory component will test the participants’ ability for cued recognition memory by using a sample of pictures—these skills are associated with attention and episodic memory. After participants have studied the pictures, the experiment will begin and the participants must determine if the pictures were studied in the primary set of pictures. Composite Face Recognition will be used to assess attention within the context of higher-level processing. This task requires participants to determine if familiar celebrity faces are aligned or misaligned.

Hypotheses

It is hypothesized that long term use of opioids will cause measureable impairments in the domains of cued recognition memory, attention, and inhibition. These deficits will manifest as declines in processing speed, as will be measured by the go-no-go, flanker arrow, cued memory, and composite face recognition tasks. We expect that participants in the opioid group to demonstrate: 1) more false alarms and a slower processing time in the Go-No- Go task, 2) an increase reaction time when given more cues, when compared to few cues, in the Cued Memory task, and 3) slower processing speed than the average person, even when the arrows are congruent, in the Flanker-Arrow task and Composite Face Recognition Task.

Experiments

Participants

Participants in the experimental group will include 25 middle-aged adults who have been prescribed opioid-based pain medication (e.g., hydrocodone) for a period of 3-6 months. Participants will be recruited from a random sampling through Health West, Inc. database in Pocatello, Idaho. In order to qualify for eligibility, participants are required to be between 20 and 55 years of age, have previous use of prescription opioid pain medication for at least six months, and have normal or corrected-to-normal vision. Each member will sign a consent and release of information form approved by the university institutional review board.

A control group will contain 25 age-matched participants who will be selected by from the Idaho State University campus and Pocatello, Idaho area. Participants included 25 middle-aged adults (mean age 31) for the cued memory task—a subset of which (five) participated in the other executive function tasks: 1. Go-no-go, 2. *Flanker-Arrow Task, and 3. Composite face recognition*. (Data collection is currently in progress for a larger study longitudinal study).

In order to participate, individuals in the control group must have no history of opioid use and normal or corrected-to-normal vision. Each member will sign a consent form approved by the Idaho State University institutional review board (IRB). The study will be established by gathering baseline data immediately upon onset of opioid pain medication use, again after a 6-month to one-year period, and again after a one-month period of abstinence from opioids.

Materials

The Behavior Rating Inventory of Executive Function - Adult Version (BRIEF-A) will be administered to participants according to the test guidelines. The BRIEF-A is a standardized test for both men and women between the ages of 18 and 90 across a wide range of social and demographic context. It includes a Self-Report Form, an Informant Report Form, and a two-sided Self-Report and Informant Report Scoring Summary Profile Form (Rothet al., 2005). The Self-Report Form and the Informant Report Form include instructions on how to properly record information. It is preferred that the Informant Report Form be administered to a knowledgeable informant, such as a family member, who has frequent face-to-face interaction (at least twice per week) with the participant completing the Self-Report Form. Additionally, the Scoring Summary/Profile Form is scored by the clinician according to the instructions that are included on the form. The test will be scored in accordance to the BRIEF-A professional manual.

In order to examine the extent to which opioid use affects multiple domains of executive function, the BRIEF-A will be administered using standardized and normed self-report measures. The scores will be composited to correlate measurements from associating studies regarding opioid use and sensory integration and central auditory impairment. Experiments 2 through 5 (described below) will be implemented in the PIs laboratory using E-Prime 2.0 Psychology Tools Experimental Software.

Experimental Procedures

1. *Go-No-Go*

The materials for this study will include a flat screen Dell computer with a refresh rate of 60 Hz to present the stimuli and a computer mouse. The stimuli will include a white horizontal or vertical bar that will flash in the center of the computer monitor for 100 ms. Participant will press the button on the computer keyboard labeled “yes” with their dominant index finger on “go” trials as quickly and as accurately as possible, and withhold their response on “no-go” trials. The stimulus for the “go” reaction will be random yet pre-determined. The “no-go” response will require participants to withhold their response. The experiment will consist of 120 trials total, 80% of which are “no-go” responses, and 20% “go” responses.

2. *Flanker-Arrow Task*

Each trial will being with a white dot appearing in the center of the computer screen indicating that the test will begin when the spacebar is pressed on the computer keyboard. The stimuli will include five arrows that will appear on the top or bottom of the screen in either congruent (same place as the arrows) or incongruent (opposite the arrows) asterisk-cue. Additionally, the arrows flanking the middle arrow either point congruently or incongruently. The arrows will be presented on the screen for 500 ms.

Participants will then be presented with 120 trials, including 60 in which the cue is congruent (same position on the screen as the arrows) and 60 in which the cue is incongruent (position of arrows and cues mismatch). The participants will be required to indicate the direction (right or left) of the middle arrow as quickly and as accurately as possible via button press.

3. Composite Face Recognition (Inhibition/Attention)

Prior to this experiment, subjects will be asked if they are familiar with Kristen Stewart and Julia Roberts. Participants will be presented with one of the two celebrity faces. In the study phase, participants will learn what button to press, ‘m’ or ‘z,’ through trial and error. In the test phase, four asterisks will appear next to either the top half, or the bottom half, of the persons face. The participant will be required to judge whether the half of the face (top or bottom) is Julia Roberts or Kristen Stewart, by button response mappings on the keyboard learned in the study trial.

After this test segment is complete, the process will continue but, rather than being presented celebrity faces, two unfamiliar faces will appear. Again, the participant will learn what face response mappings through trial and error. The participant will then judge who the person is whether the cue is pointing to the top or bottom half of the face. Additionally, the test phase contains two manipulations: match/mismatched and aligned/misaligned. The match/mismatch portion of the test phase will either align both portions of the face (match) or place the top half of face 1 and align it with the bottom half of face 2, or vice versa (mismatch). The aligned/misaligned portion of the test will require participants to determine if the faces align or are spatially misaligned (top half is slightly horizontally displaced). The participants will be presented with 200 trials in which half of the faces will be misaligned and/or mismatched. The trials are presented until the participant presses a button.

4. Cued Memory (Recognition Memory)

Participants will be shown 24 pictures, one at a time for 3000 ms. A subsequent test phase will then be presented in which the initial pictures presented in the study phase, along with 24 additional pictures, will appear one at a time for a maximum of three seconds. Each trial will require participants to indicate whether the picture was in the study phase or not. If the trial was in the study phase, the participants will be required to indicate a yes response by pressing the letter ‘m’ button on the keyboard as quickly and as accurately as possible. If the participant does not recognize the picture (was not in the test phase), he or she will make a no response by pressing ‘z’ as quickly and as accurately as possible. Additionally, some trials will present the stimulus using four cues (entire picture), three cues (three-quarters of the picture), or two cues (half the picture). This study will include a total of 48 pictures in the test phase, 24 of which are included in the study phase.

Results

Measures of the Cued Memory Task

The Cued memory task was administered to assess processing speed and episodic memory. This type of memory requires a higher form of cognitive ability because it requires the individual to recognize an object in a test phase based on the number of cues available. To perform this task, participants are required to distinguish old from new photos based on complete information versus partial information. Complete information, in this task, would mean the participant was able to view the entire picture present, or four cues. Partial information requires that patients distinguish between the old and new photos using two or three cues.

Hazard Functions and Capacity

An important aspect of our study involves the implementation of a measure capturing the idea that learning involves the increasingly efficient use of cognitive resources. This is done by measuring capacity and examining the data at the level of the hazard function. The hazard function provides the probability that a process will be completed in the next instant in time, given that it has not yet terminated by time t. The hazard function is written as the probability density function of RTs (f(t)) divided by the survivor function (1-F(t)), which denotes the probability that a process will be complete in the next instant of time given that it has not yet finished.

Cox Regression

The Cox Regression Model is based on proportional hazards models, which are a class of survival models in statistics. Survival models can be viewed as consisting of two parts: the underlying hazard function and the effect parameters. The purpose of the proportional hazard model regression is to test for ordering of two or more hazard functions derived from different experimental conditions. Cox regression essentially transforms the proportional hazard function into linear regression. Here, and independent variable (i.e., experimental conditions) may serve as a predictor, while the RT's obtained from these conditions serve as the data or "y" variable. Proportional hazard model regression is based on a log-linear regression procedure. Furthermore, Cox regression model is used for measuring reaction time.

Figure 1A: *Cox Regression*

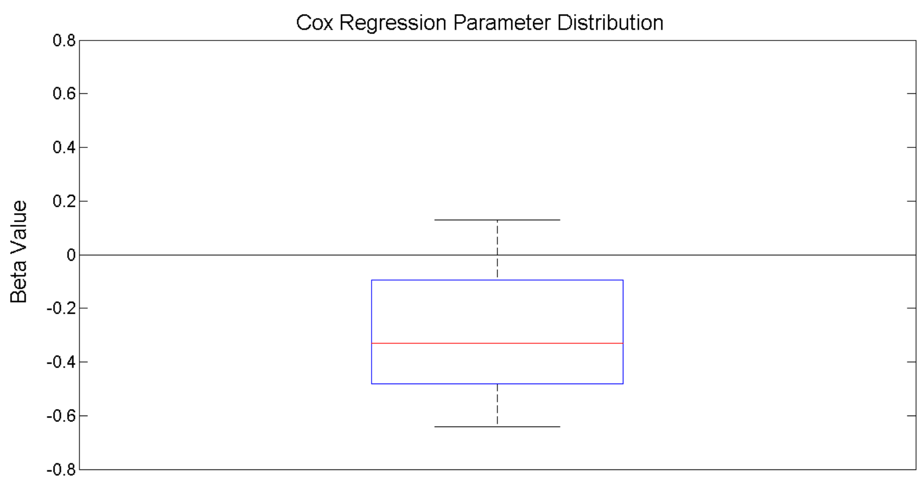

Table 1B: Mean values from the Cued Memory Task when provided complete or partial information.

Beta	4 Cues	2 Cues	1 Cue	Z	SE	Acc	p
-0.29	789.7985	833.5009	921.0029	-1.60131	0.188	0.913	0.25
0.231512	108.4771	93.49155	97.10407	1.212573	0.015	0.06	0.33

Table 1B shows the mean values of the Cued Memory Task given the variable numbers of cues. The beta indicates the slope of the line. A beta different from zero indicates that the regressor variable is significant. The table shows that the majority of subjects show a negative beta value. Furthermore, the response times were slower on average when partial information was provided compared to when complete information was provided.

Measures of the Go- No- Go Task

The Go-No- Go Task was administered to assess the executive function skills of inhibition and processing speed. The results include data obtained from five adult control participants, all without a reported history of neurological impairment. The comparison that will be carried out with the experimental control will be a comparison of mean reaction times. This will be tested by using a one-way ANOVA. Hits and false alarms will also be compared using a one-way ANOVA. It is hypothesized that the control group will have faster reaction times and lower false alarms.

Table 2A: Mean reaction time, hits, and false alarms among participants on the Go-No-Go Task

Table 2A above shows the mean RT time for all sample control participants, as well as the Hits and False Alarms. Generally participants had a hit rate of over 90% and false alarm rates

to be about one percent. One participant was omitted because it appeared he did not understand the task

Measures of the Flanker Arrow Task

Participant	Mean Reaction Time	Hits	False Alarms
1	418.033	0.967	0.05
2	424.933	0.967	0.025
3	412.733	0.967	0
4	339.967	0.733	0
5	500.4	1	0.017
	Total RT (Mean)	Total Hits (Mean)	Total FA (Mean)
	419.21	0.92	0.018

Figure 3A shows box-plots of the accuracy scores for the Flanker Arrow Task comparing a congruent arrow, neutral arrow, and incongruent arrow using a congruent cue versus incongruent cue. The upper and lower portions of the box-plots denote the 75^{th} and 25^{th} percentiles. The middle line represents the median and the whiskers represent 1.5 times the interquartile range. The + sign indicates statistical outliers that lie beyond 1.5 times the interquartile range. The mean reaction-time for the congruent arrow and neutral arrow is approximately 500 ms, whereas, the mean reaction time for the incongruent arrow is approximately 550 ms. Overall, the mean reaction times did not demonstrate significant differences in RTs between conditions for the control participants; however, there was a non-significant trend toward faster responses in the neutral and congruent versus the incongruent condition. The repeated measures ANOVAS are presented in Table 3B.

Figure 3A: Box-Plots of the accuracy score of the Flanker Arrow Task comparing a congruent arrow, neutral arrow, and incongruent arrow.

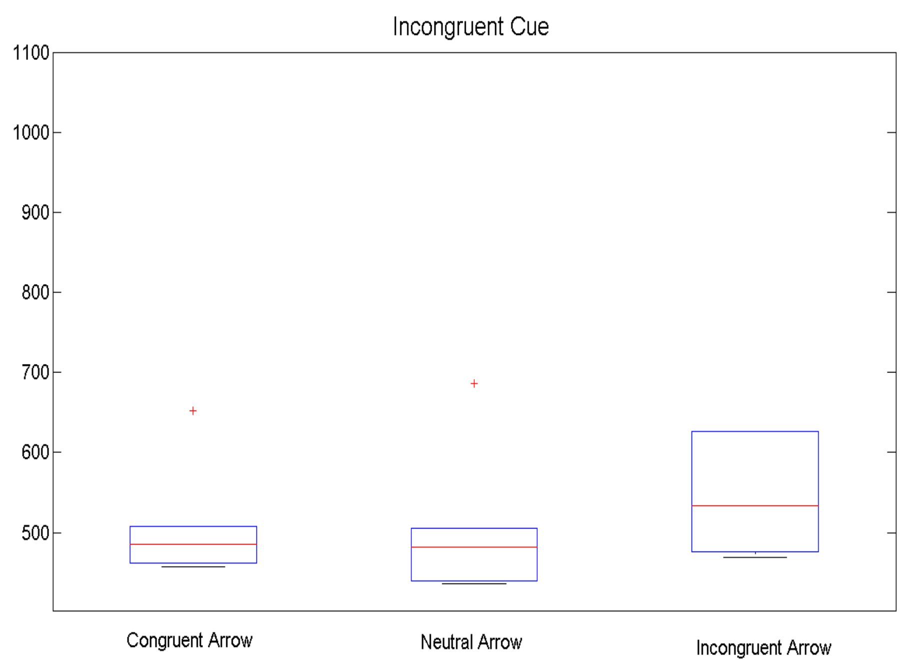

Table 3B: Repeated measures ANOVAs for the Flanker Arrow Experiment. Arrow congruency, and cue congruency were the factors.

Source	df	F	F
Arrow Congruency	2	1.93	0.1712
Cue Congruency	1	0.07	0.8017
Interaction	2	0.45	0.6409
Subjects	10	0.71	0.708

Error	20		
Total	35		

When comparing congruent and neutral arrows, there was a lack of significant advantage with reaction-time; however, both congruent and neutral arrows had a marked decrease in reaction time when compared to the incongruent arrow. The ANOVA table (Table 3B above) indicates that there is a trend for arrow congruency but the numbers are insignificant. The primary cognitive subscales that are tested in the flanker-arrow task are attention and inhibition. Attention involves focusing on a particular task while inhibition requires impulses.

Measures of the Composite Face Recognition Task

This task consisted of eight conditions listed in table 4A below. The conditions consisted of a combination of famous or non-famous faces, aligned or misaligned, and congruent or incongruent. The mean reaction and mean accuracy of each condition is shown below. In this task, the effects of congruency for facial identity and facial alignment across familiar and unfamiliar faces were investigated. To examine whether there was a trend of significant effects within this control group, measured repeated measures ANOVA was carried out. The results indicated a marginal effect for conditions (aligned congruent, aligned incongruent, misaligned congruent, misaligned incongruent; $F(3,24) = 2.8$, $p = .06$). Overall, based on mean reaction times, it appears that participants responded to congruent identity faces faster than incongruent faces. Mean reaction times also indicated that familiarity of famousness also demonstrated null effect ($F(1,24)=1.12$, $p=.3$).

Table 4A: Mean RT, Mean Accuracy, and conditions in the Composite Face Recognition Task

Condition	Mean RT (SE) in ms	Mean Accuracy (SE)
Familiar		
Aligned, Congruent	905 (87.9)	0.98 (0.01)
Aligned, Incongruent	940 (66.8)	0.91 (0.04)
Misaligned, Congruent	929 (47.7)	0.94 (0.03)
Misaligned, Incongruent	941 (55.1)	0.96 (0.01)
Unfamiliar		
Aligned, Congruent	984 (80.6)	0.93 (0.02)
Aligned, Incongruent	1067 (84.7)	0.81 (0.09)
Misaligned, Congruent	1028 (70.2)	0.86 (0.06)
Misaligned, Incongruent	1062 (87.6)	0.81 (0.09)

Discussion

There is a significant gap in knowledge concerning the extent to which sensorineural dysfunction caused by opioid use relates to changes in higher cognitive function and language perception. In other words, the changes in language perception and executive function may strongly correlate to changes in auditory sensory function, or vise-versa.

Previous research studies have revealed a significant relationship between opioid use, and changes in cognitive functioning based on performance on fluid intelligence tests and poor working memory and executive functioning (Jongsma et al., 2011; Marvelm, Faulkner, Strain, Mintzer, & Desmond, 2012; Rapeli et al., 2006; Singh, Basu, Kohli, & Prabhakar, 2009). Studies have also concluded that cognitive deficits may continue even after short periods of abstinence from opioid medications (Rapeli et al., 2006); this points to the need for a more developed longitudinal study on opioid use and executive functioning skills. The continuation of this project will bridge the gap between the relationship of opioid related sensorineural dysfunction and changes in higher cognitive function and language perception. Furthermore, auditory sensory function, speech recognition ability, and executive function will be correlated to determine the extent to which they predict one another.

This study contains multiple hypotheses. First, it is hypothesized that the opioid group will show deficits in inhibition and processing speed. This will be evidenced by longer response times on "go" trials and more frequent false alarms on the "no-go" trials when compared to the control group. For this study, the control participants performed a predicted reaction time, hit rate, and false alarm rate.

In the flanker arrow task, the controls should have relatively similar times for all the different arrow directions; however, in the opioid group, it should show a greater discrepancy due to the lack of attention and inhibitory control. This hypothesis is expected with our findings in the flanker arrow-task. It was found that the mean reaction times among the control group did not demonstrate significant variability depending on the direction of the arrows, although incongruent arrows had a slight increase in reaction time.

For the composite face task, it is hypothesized that the opioid group will show slower response times for mismatched compared to the control group faces due to their poorer ability to focus attention and ignore conflicting information from the mismatched face. Additionally, the experimental group should show a greater difference in processing times as a function of face-familiarity. Specifically, "The famous face effect" indicates that famous faces are recognized because a template of them is stored in memory; hence, they are likely processed differently than unfamiliar face. In the context of this study, it is hypothesized, that the reaction times for identifying mismatched faces of celebrities will be increased compared to the identifying the mismatch of non-celebrities. For example, when comparing the mean reaction time between a mismatched picture of Julia Roberts + Kristen Stewart versus two non-celebrity faces, it is expected that the experimental group will spend more time looking at the photo of Julia Roberts/Kristen Stewart due to their familiarity. In other words, they will have a more difficult time inhibiting conflicting information compared to the control group.

For now, the results of the face recognition task indicated that the control sample exhibited faster mean reaction times when faces were congruent versus incongruent and the familiarity of famousness demonstrated null effects. These effects are predicted to be larger for the experimental group.

Finally, previous research has indicated that response times will change depending on the number of cues available. In the Wenger, Negash, and Petersen (2010) study comparing measures of capacity among individuals with mild cognitive impairment versus those without, it was observed that adding an additional cue produced a reduction in capacity for all participants. The results determined that the group with the mild cognitive impairment were especially sensitive to the effect of carrying processing load by showing significant effects, both positive and negative, for increasing the number of cues. This information is comparable to the current study in that response times were slower on average when only two or three cues were provided compared to when four cues were provided.

Future Directions

The projected plan for this project is to develop a longitudinal study that assesses auditory sensory function in conjunction with audiovisual integration skills. The purpose is to investigate the degree in which changes in auditory sensory function co-occur with changes in perceptual and cognitive domains such as auditory, visual and audiovisual speech recognition skills, and executive function. For example, changes in auditory sensory function may possibly co-occur with deficits in processing speed, as measured by executive function tasks. Integrating the data between the three studies will provide necessary information to develop pain management plans in patients that may be at risk for hearing loss or declines in cognition and communication skills.

Summary

The overall limited research regarding the long term side effects of prolonged opioid use on memory, language, and cognition is the motivation for this study. It is hypothesized that long term use of opioids will cause impairments in memory, particularly short-term memory, and executive function as measured by poorer performance on tests of inhibition, attention, cued recognition, and processing speed. These aspects are assessed by using the Cued Memory task, Go-No- Go task, Flanker Arrow Task, and the Composite Face Recognition Task while being compared to the BRIEF-A. The control sample exhibited an expected reaction time, hit rate, and false alarm rate on the go-no-go task; a non-significant mean reaction time when comparing direction of arrows in the flanker-arrow task; a faster mean reaction time when faces were congruent versus incongruent and the familiarity of famousness demonstrated null effects in the composite face recognition task; and slower response times when only two or three cues were provided compared to when four cues were provided. The continued study will investigate the degree to which changes in auditory-sensory function co-occur with changes in the perceptual and cognitive domains.

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