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Executive Function Deficits in Patients with Mild Cognitive Impairment: Exploring the Impact of Substance Use

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**EXECUTIVE FUNCTION DEFICITS IN PATIENTS WITH MILD COGNITIVE
IMPAIRMENT: EXPLORING THE IMPACT OF SUBSTANCE USE**

A Master's Thesis

Presented to

The Graduate College of
Missouri State University

In Partial Fulfillment

Of the Requirements for the Degree
Master of Science, Psychology

By

William Dooley

May 2019

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EXECUTIVE FUNCTION DEFICITS IN PATIENTS WITH MILD COGNITIVE IMPAIRMENT: EXPLORING THE IMPACT OF SUBSTANCE USE

Psychology

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Master of Science

William Dooley

ABSTRACT

Substance use is pervasive in the United States. With overdose deaths on the rise for the past decade, studies have examined the detrimental effects of a range of substances. Substance use has been shown to affect the domains of executive functioning, while diseases such as Human Immunodeficiency Virus (HIV) and Hepatitis-C (Hep-C) have been shown to increase the severity of these deficits when comorbid with substance use. Alzheimer's Dementia (AD) also affects many of the same domains of executive functioning as substance use. However, because of the rapid degenerative nature of the disease, individuals clinically determined to have Mild Cognitive Impairment (MCI) with a risk of progression to AD are more uniform in symptom presentation and discerned deficits, and are therefore more feasible to examine. This study examined whether a history of substance abuse impairs executive function in a cumulative manner when comorbid with MCI with a clinically indicated risk of progression to AD. While those subject to both MCI and substance use history did have the lowest scores in all of the assessments and in each of the conditions measured, those differences were insignificant. The hypothesis was not supported, even though the trend in scores was in the predicted trajectory. These results and implications are discussed, while limitations and possible future research directions are outlined.

KEYWORDS: executive function, substance use, mild cognitive impairment, dementia, additive effects, comorbidity, Digit Span, Trail Making Test, COWAT

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In the interest of academic freedom and the principle of free speech, approval of this thesis indicates the format is acceptable and meets the academic criteria for the discipline as determined by the faculty that constitute the thesis committee. The content and views expressed in this thesis are those of the student-scholar and are not endorsed by Missouri State University, its Graduate College, or its employees.

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INTRODUCTION

Drug Use on the Rise

There has been much focus in the last few years, particularly in the media, on the harms and growing crisis of opioid use and dependence (Rice, 2018). While drugs like Fentanyl and Heroin receive considerable attention, other equally dangerous substances like methamphetamine are largely forgotten (Robles, 2018). There are, however, indications that methamphetamine use is becoming more prominent again. The Substance Abuse and Mental Health Services Administration (SAMHSA) released a report detailing the trends in methamphetamine use amongst Americans. While initial methamphetamine use was on a general downward trend for the entire decade of 2000-2010, it has either remained stable or increased for every subsequent year (SAMHSA, 2017). In fact, just over 100,000 people tried methamphetamine for the first time in 2010, a number that jumped to 144,000 in the year 2013 (SAMHSA, 2017).

Supplementing those numbers is a report from the Center for Disease Control and Prevention (CDC) noting that the rate of overdose deaths involving methamphetamine tripled between 2011 and 2016 (Hedegard et al., 2018). Furthermore, arrests and seizures of methamphetamine are on the rise across the country (Robles, 2018). According to the National Institute on Drug Abuse (NIDA), over 5% of individuals 12 and older have tried methamphetamine in their lifetime, and more than 1 in 10 of those individuals have used within the last year (NIDA, 2018). These figures foreshadow the detrimental effects methamphetamine use will have on the population, should trends continue in the same direction and magnitude that they currently are.

Methamphetamine and opioids are not the only drugs being used with detrimental effects. Of the 135 million people aged 12 and over in the US who admitted to current alcohol use, almost half of them report binge drinking in the past month (SAMHSA, 2017). Binge drinking is

defined as consumption of five or more drinks for males (and 4 or more for females) on the same occasion (SAMHSA, 2017). Even though alcohol use trends have stayed relatively stable in the past few years, and even declined in some aspects, the effects of alcohol abuse still costs our nation 250 billion dollars annually (NIDA, 2018). Overdose deaths attributed to a variety of drugs has also been on the rise in the past decade. Cocaine, Benzodiazepines, and antidepressants overdose deaths have been driven up in large part due to their mixture with opioids, although cases involving no other opioids have also seen an increase in recent years for these drugs (NIDA, 2018).

Deficits Stemming from Use

Aside from the obvious life-altering legal or even deadly consequences listed above, drug use has well documented detrimental effects on individuals. From an etiological perspective, however, it is difficult for researchers to discern deficits associated with specific drugs, due to the majority of abusers using more than one substance (Fernandez-Serrano et al., 2010). Impairment in general function domains of the brain may be compounded by polysubstance use (Fernandez-Serrano et al., 2010; Meredith et al., 2005).

NIDA (2018) notes that substances of abuse increases the amount of dopamine in the brain. Dopamine reinforces drug-taking behavior, and this makes these substances highly addictive. Chronic use results in an overactive dopamine system, and causes changes in structural and functional domains of the brain (NIDA, 2018). One of the most studied domains is executive function, which many researchers agree is detrimentally affected by substance use (Bechara & Martin, 2004; Garcia-Fernandez, Garcia,-Rodriguez, & Secades-Villa, 2011; Henry, Minassian, & Perry, 2010; Meredith, et al., 2005; Simon, et al., 2000; Van Holst & Schilt, 2011;

Yucel et al., 2007). This finding has been corroborated in adolescent users of methamphetamine as well (King et al., 2010). Executive functioning consists of multiple domains, which work together to allow individuals to manipulate and navigate ideas, thoughts, and challenges (Diamond, 2013). Working memory is one aspect of executive functioning consistently studied for assessing the extent of impairments in methamphetamine users (Bechara & Martin, 2004; Hoffman et al., 2006; Simon et al., 2000).

One of the most significant issues for researchers in this area is linking deficits to specific drugs. As mentioned before, this stems in large part from the majority of users being polysubstance abusers (Fernandez-Serrano et al., 2010). In a recent meta-analysis examining drug-specific neuropsychological impairments, none of the drugs examined, except alcohol, had more than two studies available that met criteria for 'pure' users of specific drugs (Fernandez-Serrano, Perez-Garcia, & Verdejo-Garcia, 2011). Exacerbating this is the fact that many other drugs have been found to impair executive functioning as well (Garcia-Fernandez, Garcia-Rodriguez, & Secades-Villa, 2011; Pluck et al., 2012; & Woicik et al., 2009).

While the drug-specific deficits do not completely overlap one another, their collective impairment of executive function would be identifiable on measures of general executive functioning in neuropsychological assessments. This is the case whether the individual is a polysubstance user or a single substance user, although Nixon (1999) notes that polysubstance abuse may cause more adverse neuropsychological effects than single substance abuse. Fernandez-Serrano (2011) found that even when the main drug of choice was different, most of the impairments between groups of polysubstance users were shared.

These impairments of executive function contain many practical consequences. Fernandez, Rodriguez, and Villa (2011) note that changes in executive functioning caused by

drug use can affect psychosocial functioning, the course of an addiction, and even the success of any eventual treatment. In other words, the changes of executive functioning due to substance use have very real implications in how individuals move forward with their lives. Van der Plas et al. (2009) also found that gender and drug of choice can contribute to the differing effects that drug use has on executive functioning, suggesting that men and women who use substances might experience differing effects.

In one study investigators found methamphetamine dependence was associated with a decrease in everyday functional ability, particularly in the areas of comprehension, finance, transportation, communication, and medication management, when compared to drug free participants (Henry, Minassian, & Perry, 2010). A meta-analysis on a variety of drug use studies found that all abused drugs, except cannabis, showed association with lowered inhibition (Van Holst & Schilt, 2011). Alcohol was found to specifically affect working memory and visuospatial abilities (Van Holst & Schilt, 2011). In a task involving delayed rewards, methamphetamine users were also found to discount a reward that would be delayed more than non-users (Hoffman et al., 2006). This impulsivity was correlated with memory deficits resulting from methamphetamine use, rather than any non-drug induced psychological impairment. The authors suggest that it was also not associated with any other drug use history variables that were tested or measured, such as nicotine use or marijuana use (Hoffman et al., 2006).

Many of the neurocognitive impairments that come from drug use are dependent upon dose and duration of use, and there are many short and long term effects of using (Meredith et al., 2005; NIDA, 2018). Although single doses of an amphetamine can actually improve performance in several neurocognitive domains, chronic users normally experience multiple

neurocognitive impairments (Meredith et al., 2005). Bechara and Martin (2004) identified some of these impairments when they compared individuals that primarily used alcohol, meth, or cocaine against non-users. They found that a number of individuals formed a sub-group who performed as well as non-users, but the overall groups had below normal levels of performance on both decision making and working memory measures.

Although this study sought to identify impairments shared among abusers of different substances, the study yielded interesting results. Methamphetamine users comprised the majority of the impaired individuals subgroup, and were more severely impaired than individuals who abused the other substances examined (Bechara & Martin, 2004). They concluded that these deficits were attributed to the executive process of working memory only, rather than an impairment of short term memory processes (Bechara & Martin, 2004).

Other studies have identified impairments that are specific to certain substance users. Opiate users appear to particularly be affected in areas of verbal fluency, and cocaine users were found to have lower cognitive flexibility (Van Holst & Schilt, 2011). Abusers of almost every illicit drug develop impaired verbal memory (Meredith et al., 2005). Methamphetamine users also become impaired on tasks of perceptual speed, manipulating information, and tasks that combine these skills with visuomotor scanning (Meredith et al., 2005).

Abstinence

Much of the research cited has focused on active substance users, but there is also a host of research that examines what occurs in users following various periods of abstinence. Multiple researchers have found that methamphetamine users who are abstinent actually perform more poorly on measures of neurocognitive impairment in the initial phases of abstinence

(Kalechstein, Newton, & Green, 2003; Meredith et al., 2005). These studies found deficits in domains such as attention, psychomotor speed, verbal learning and memory, and executive functioning in users that had been abstinent for a range of 5-14 days. One of the studies, by Kalechstein, Newton, and Green (2003), focused on ensuring that these impairment levels were properly attributed to use and abstinence of meth, and not confounding variables, such as demographic variables, estimated premorbid IQ, or self-reported depression.

The other article, a meta-analysis, noted that scores on psychomotor and verbal memory tasks were initially worse during early abstinence. Between 3 and 14 months of abstinence, they suggest that a slight improvement in these scores was detected, although this change is short of any statistical significance (Meredith et al., 2005). Even after an average of eight months of abstinence, former users still performed significantly worse on tasks measuring working memory. The authors suggest the decrements in these domains never significantly recover, even after extended periods of abstinence. Similarly, one meta-analysis which consisted of studies requiring two weeks of abstinence, found impairments involved with opiates, alcohol, meth, and cocaine, although these studies did not compare performance to pre-abstinence values (Van Holst & Schilt, 2011).

Data from other studies suggest that substance users exhibit less impairment after periods of abstinence. Simon et al. (2010) found that methamphetamine users performed better on cognitive tasks after one month of abstinence, although those results were not statistically significant. They also found that no considerable cognitive gains were made after the first month of abstinence, although they suggest that longer periods of abstinence may result in significant cognitive improvement (Simon et al., 2010). Consistent with this theory that longer periods of abstinence are associated with significant improvements in cognition, some studies have found

that extended abstinence can facilitate a period of neuropsychological recovery. These periods of recovery may unfold over as long as one year, and longer abstinence was associated with greater improvement of cognitive functioning. It should be noted this finding was not statistically significant in that time frame (Iudicello et al., 2010). Mann et al. (1999) found that the discrepancies of neuropsychological functioning between a control group and group of alcohol dependent individuals were lowered to non-significant levels after several weeks of abstinence.

More research is necessary to determine the extent or even the possibility for reduction of deficits in cognitive functioning due to substance use. Even without significant cognitive domain improvement, longer-term abstinence has also been associated with improvement in mood and overall emotional distress in individuals, making abstinence from drugs beneficial across multiple aspects for individuals (Iudicello et al., 2010).

Critiques

The previous findings reported are not universally accepted and other researchers have found conflicting results. Hart et al. (2012) claim the results from many studies on methamphetamine use show no significant differences on the majority of cognitive tasks. In those studies where significant differences with a comparison group have been found, results for the substance using group still fall within the normal range of scores for age and education demographics. Further they claim that if methamphetamine use caused deficits in the brain, then these deficits should be immediately apparent after administration of the drug, and not only after chronic use of it (Hart et al., 2012). For instance, Johanson et al. (2006) found methamphetamine users performing lower than non-users on 3 of 12 tasks administered, and

those participants still performed within normal range. They also determined that length of abstinence was not correlated with substantial changes in neurocognitive functioning (Johanson et al., 2006).

Other studies have found similar results. Simon et al. (2000) found methamphetamine users to perform more poorly than control groups on some measures (word and picture recall, Digit Symbol, Stroop Color Word Test and Trail Making Test Part B), but found no significant differences on other tests (Shipley Hartford Vocabulary Test, The Wisconsin Card Sort Test, FAS Verbal Fluency Test, and the Backward Digit Span Test). In a separate study the authors argued most researchers base their results on null hypothesis statistical significance testing, but that using effect size analysis produces a more accurate picture of any impairment, and is more consistent with results produced by neuroimaging studies (Jovanovski, Erb, & Zakzanis, 2005).

One study found that some methamphetamine users were neuropsychologically impaired, while others performed within the normal range of functioning (Mariana et al., 2010). This study ensured users were free of HIV/HEP C, which are known to compound neuropsychological deficits, and that they were similar in age of first use, total years of use, route of consumption, and length of abstinence. They suggest that their findings are indicative of the need for more research into individual vulnerability differences for the neurotoxic effects of methamphetamine use (Mariana et al., 2010).

Discerning and Explaining Deficits

The majority of researchers agree, however, that “some” deficits arise from chronic substance use. Much of the evidence for impairments in executive functioning has been identified either by traditional neuropsychological assessments or by neuroimaging. Multiple

studies cite the Wisconsin Card Sort Test (WCST) as the instrument for assessing impairments (Henry, Minassian, & Perry, 2010; Meredith et al., 2005; Simon et al., 2000). Meredith et al. (2005) noted that methamphetamine users scored more poorly than either cocaine or heroin users on the WCST. Simon et al. (2000) however, found no significant differences between users and a control group on either WCST scores or scores on the Shipley Hartford Vocabulary Tests, the FAS Verbal Fluency Tests, or the backward digit span test, although they did find significant differences on the Digit Symbol, Trail Making Part B, and Stroop Color Word Test tasks. Other studies utilized the Trail Making Tests, Stroop Color Word Test, Digit Span tests, Letter-Number Sequencing, Peg Board Tasks, and Wechsler Matrices tasks (Kalechstein, Newton, & Green, 2003; King et al., 2010).

As implied in the nomenclature of neuropsychology, these observed deficits have a biological basis. NIDA (2018) notes that drugs increase the amount of dopamine in the brain and causes damage to nerve cells. Long term use changes dopaminergic neurons, by displacing the dopamine and reversing its transport, ultimately leading to extracellular levels of the neurotransmitter (Johanson et al., 2006; Nordahl, Salo, & Leamon, 2003). Meredith et al. (2005) state that poorer scores on assessments are indicative of frontal lobe dysfunction, a sentiment echoed by other researchers for a variety of different drugs (Garavan & Hester, 2007; Henry, Minassian, & Perry, 2010; Verdejo-Garcia et al., 2006). Other studies have identified specific areas of the prefrontal cortex measured in assessments (dorsolateral prefrontal cortex, orbitofrontal cortex, and the anterior cingulate cortex) and found a generalized pattern in abnormal performance associated with all three of these domains after use (Verdejo-Garcia et al., 2006).

Others suggest brain abnormalities are slightly different in nature, specifically that the frontostriatal and limbic systems are the most affected (Iudicello et al., 2010). Nordahl, Salo, and Leamon (2003) point out that serotonin has been shown to be affected when monkeys are injected with methamphetamine, but that there have been no neuroimaging studies on humans to determine if they are affected in the same way. They note that neuroimaging has supported the notion that methamphetamine use causes damage to multiple transmitter systems throughout the brain, although no studies of this type have been conducted to determine reversibility or permanency of damage (Nordahl, Salo, & Leamon, 2003). Meredith et al. (2005) state that the specific biological markers of a brain impaired by substances persist into abstinence, however. A number of studies have also utilized neuroimaging to determine deficits in individuals who abuse alcohol (Petit et al., 2014; Tapert et al., 2001)

Combined Effects

An important aspect of substance use to consider is the occurrence of Human Immunodeficiency Virus (HIV) and Hepatitis C (HEP-C). Both of these disorders are associated with drug use, particularly drugs that may be administered intravenously. HEP-C is the most common blood borne infection in the United States, with almost 3 million people being affected (Kim, 2002; Martin-Thormeyer & Paul, 2009). More than a quarter million of those individuals also have a co-infection with HIV (Martin-Thormeyer & Paul, 2009). Although HIV and HEP-C are qualitatively different infections, they are identified as a group here and in other studies due to their similarities in possible infection stemming from the same types of behaviors, and similar detrimental effects on cognition. Drug users are more susceptible to diseases such as HIV/HEP-C, in part because of risky behaviors such as needle sharing or unprotected sex (NIDA, 2018).

Methamphetamine use, HIV, and HEP-C all affect neuropsychological functioning by damaging the Central Nervous System and causing impairment (Letendre et al., 2005). Likewise, alcohol abuse has been associated with an additive effect on neuropsychological impairment when present with HIV in an individual (Rothlind et al., 2005). Use of these substances exacerbates the effects of HIV/HEP-C by causing more damage to nerve cells than would otherwise be the case without drug use (NIDA, 2018). Thus, HIV and HEP-C have an “added” or “synergistic” effect on neurocognition when comorbid with each other or when either is comorbid with drug abuse (Chang et al., 2005; Cherner et al., 2005; Martin-Thormeyer & Paul, 2009; Rothlind et al., 2005). It is possible that this same principle is true when substances are comorbid with other disorders/illnesses that affect executive functions.

Dementia and Aging

Alzheimer’s type dementia (AD) is characterized specifically by deficits in executive functioning that become progressively worse over time (Robbins, Elliott, & Sahakian, 1996). At least two cognitive domains must be impaired to be identified as such, and one of those must be memory. The other impaired domain may be language, praxis, visual perception, attention, or problem solving (Robbins, Elliott, & Sahakian, 1996). Many of the most common tests for evaluating specific executive functioning deficits in aging are used to assess the same specific deficits in substance use, namely: Trail Making Test B, Verbal Fluency Test (FAS), VFT-Animals Category, Digit Span (WAIS), Stroop Test, and the WCST (Faria, Alves, & Charchat-Fichman, 2015). These tests assess deficits in verbal fluency, working memory, planning, and inhibitory control.

AD is a rapid progression disease, with the average person living between 4 and 8 years after diagnosis, and is by far the most common form of dementia (Alzheimer's Association, 2018). From a treatment perspective it is imperative to recognize early symptoms and warning signs. Because AD progression is so rapid and degenerative, the effects are particularly devastating. Although symptoms for those affected by AD can be typical and follow a general pattern, the quick decline and numerous areas of functioning that are affected (Stucky, Kirkwood, & Donders, 2014) make it very difficult to compare multiple patients' symptoms to each other, particularly in a study such as this comparing the mean functioning of multiple groups.

Mild cognitive impairment (MCI) is used, in part, to define the transition period between normal aging cognitive changes and the onset of dementia (Peterson, 2003). When cognitive changes greater than what can be attributed to normal aging are detected, but not meeting the criteria for AD, a diagnosis of MCI is considered warranted. The diagnostic criteria include behaviors and symptoms that must be present, as well as the absence of certain symptoms and behaviors. In some ways the criteria for MCI are more uniform than those for AD.

Not all MCI-diagnosed patients will develop dementia, and the only way to definitively diagnose AD is through neuropathological examination of brain tissue (Stucky, Kirkwood, & Donders, 2014). There are, however, clinical indicators that point to the likelihood of a patient with MCI progressing to a diagnosis of AD. The clinician treating the patient is responsible for utilizing multiple methods to examine the symptoms and interpret the likelihood of an AD diagnosis. This is an important distinction as when a comprehensive examination is performed, a clinical diagnosis of AD is 85-90% accurate (Stucky, Kirkwood, & Donders, 2014).

It may be possible for disorders that lead to deficits in executive functioning to have a synergistic effect when comorbid with a history of drug use, just as HIV or HEP C do. Executive functioning impairments caused by MCI with a clinical indication of AD may be exacerbated when an individual has a history of substance abuse. While there has been considerable research on many aspects of AD, there does not appear to be any examination of the possible additive effects when MCI with a clinical indication of AD occurs in tandem with a history of substance use. This is noteworthy, given the current demographics and statistics associated with aging and dementia. AD is the sixth leading cause of death nationally and the only one for which there is no cure. (Alzheimer's Association, 2018). Nearly 6 million people live with Alzheimer's in the United States currently, a figure that is expected to triple in the next 30 years, as the number of individuals 65 and over grows to exceed 20% of the total population (Alzheimer's Association, 2018; Benschoff, Harrawood, & Koch, 2003). This leaves potential for many problems, especially considering the "Baby Boomers" history with drug use (American Addiction Centers, 2018).

If research supports evidence that substance use combined with clinically indicated MCI interact to impair neurocognitive function, many avenues of research into early stage interventions to slow decline could be possible. There also could be a better understanding into risk factors for decline in individuals with a history of substance use. This serves as a basis for the hypothesis in this study, namely that MCI patients with a history of substance use will have significantly lower scores on measures of executive function than both of the 'subjective memory loss' groups with or without substance use, as well as the MCI group without a known history of drug use. The 'subjective memory loss' groups will consist of individuals who presented with memory complaints, but did not meet the criteria for a diagnosis of MCI.

METHOD

Research Design

The purpose of this study was to explore in more detail the relationship of substance use history and executive functioning impairment among individuals with Mild Cognitive Impairment (MCI). A between-subjects design was employed, separating participants into one of four conditions: Subjective Memory Loss without Substance Use History was used to measure participants without the presence of either variable; Subjective Memory Loss with Substance Use History and MCI diagnosis without Substance Use History were used to measure the influence of either variables; and MCI diagnosis with Substance Use History measured the combined effects of the variables. As the data used for this study were archival, random assignment was not possible. Records from an outpatient clinic were reviewed and participants were designated to their respective condition based on diagnosis they received and their past history of substance abuse. Although 200 participants were initially expected for this study, only 101 former patients were found to meet the criteria for inclusion. This study was approved by the university IRB (see Appendix).

Participants

Data were gathered from archival files of 101 patients from a clinic located within a local hospital. All were patients seen by one of three providers within the last seven years. Thirty-four participants (34%) were found to meet the criteria for inclusion in the Subjective Memory Loss without Substance Use condition; 46 (46%) were included in the MCI diagnosis without Substance Use condition; 11 (11%) were included in the Subjective Memory Loss with

Substance Use condition; and only 8 (8%) were found to include in the MCI diagnosis with Substance Use condition. Data from two participants were deleted due to not meeting the age limit parameter for this study, making a total of 99 participants with valid data. Participant ages ranged from 56 to 89, with a mean age of 71. Fifty-six (56%) participants were male, and 43 (43%) were female. Due to the nature of the records reviewed, ethnicity and education were not able to be determined. This information was stripped of all identifying information except age and gender.

Materials

All test scores recorded were from a standard subjective memory complaint battery for older adults used by the clinic. These are established instruments used on a regular basis at the clinic as part of a comprehensive examination to determine neuropsychological functioning, along with multiple other tests and measures. Scores are derived with a variety of methods. For the TOPF, Digit Span, and COWAT, scores are determined by the number of items an individual correctly identifies. The Trail Making Tests are scored by the length of time it takes to complete them. Therefore, higher raw scores on these tests indicate worse performance. Assessment scores for this study were standardized in order to analyze them uniformly, as well as to eliminate any confusion with reported reverse-scored assessment outcomes.

Test of Premorbid Functioning. The Test of Premorbid Function (TOPF) is used to assess an individual's level of cognitive functioning and compare it with a predicted full scale intelligence quotient (FSIQ). It is an updated version of the Wechsler Test of Adult Reading (WTAR), which has been validated as a reliable measure for assessing cognitive functioning (Mullen & Fouty, 2014). Functioning level is determined by the individual's ability to correctly

pronounce a list of words. The predicted FSIQ is based on patient demographics such as age, ethnicity, level of education, highest employment, and region of the country where the individual was born. This assessment was utilized as a means to establish the similarity of premorbid functioning among the participants. While these tests have been proven valid with a variety of populations (Green et al., 2008; Whitney et al., 2010), they have been shown to be affected by the severity of dementia in an individual (Oakley, 2012).

WAIS-IV Digit Span. The Digit Span subtest is part of the Wechsler Adult Intelligence Scale-Fourth Edition (WAIS-IV), and is a portion of the Working Memory Index score, which factors into the overall Full Scale IQ. It is administered by a clinician who recites sequences of numbers in increasing length and, therefore, complexity. After each sequence, the test participant attempts to repeat the numbers in the correct order. This subtest, and the entire WAIS-IV, has been validated in numerous studies, utilizing multiple models of intelligence (Benson, Hulac, & Kranzler, 2010; Holdnack et al., 2011).

Trail Making Tests A&B. The Trail Making Tests A&B measure different abilities within the domain of executive functioning. The participant completes this task by drawing lines between circled numbers, connecting them to the next successive number. In Trail Making Test B, both numbers and letters are present, and the participant alternates between them in successive order. The participant is scored according to number of mistakes and time to completion. These tests have been validated as measures of executive function ability (Sanchez-Cubillo et al., 2009).

Controlled Oral Word Association Test (COWAT). The COWAT is a test of verbal fluency. The clinician presents a letter, and gives the participant 60 seconds to recite as many words as they can recall that start with that letter. This is repeated three times with different

letters (at the clinic where data were collected, FAS), and the scores totaled. This test has been validated for executive function assessment (Ross et al., 2007).

Procedure

All of the participants were patients in the Neuropsychology office of a Midwestern hospital receiving services from one of three providers in the last seven years. Reports and assessment scores were kept in computer files. Researchers examined individual files to identify participants that met eligibility criteria in one of four groups: Subjective Memory Complaints with Substance Use, Subjective Memory Complaints without Substance Use, MCI without Substance Use, or MCI with Substance Use. Subjective memory complaints, for the purpose of this study, were defined as patients who presented with complaints of memory changes or loss, but were shown through comprehensive neuropsychological examinations to have no evidence of decline in memory or cognition.

Eligibility criteria included 56 years of age and older, a diagnosis of MCI with a clinical indication of progression to AD (for the MCI conditions), a history of substance use (for the substance use conditions), and no evidence of cognitive or memory decline (for the subjective memory complaint conditions). Exclusion criteria included 55 years of age or younger, a diagnosis of Hepatitis C or HIV, and diagnosis of a neurocognitive disorder other than MCI. These diagnoses included Major Cognitive Impairment, MCI due to vascular or frontotemporal etiologies, or Traumatic Brain Injury.

The demographic information and selected test scores were extracted and organized in their respective conditions in a spreadsheet with a corresponding study I.D. The tests used were part of a standard memory complaint battery used at the clinic for older adults, and included the

following: Test of Premorbid Functioning, WAIS-IV Digit Span scores, Trail Making Tests A & B, and the COWAT-Verbal Fluency Test. The latter four are tests used to measure aspects of executive functioning. Some participants were found to be missing scores for individual tests. These missing data were replaced with the overall mean score for that instrument. The number of missing data points by test were: 5 from the Test of Premorbid Functioning, 1 from the Digit Span subtest, 2 from the Trail Making A Test, 2 from the Trail Making B Test, and 1 from the Controlled Oral Word Association Test. A one-way between subjects Analysis of Variance (ANOVA) was performed to determine any difference between groups on the TOPF. A one-way between subjects ANOVA was also utilized to determine statistically significant differences between the conditions and the other assessments (Digit Span, Trail Making A&B, and COWAT), and a Bonferroni Post Hoc analysis was conducted to identify in which conditions the significant differences were found.

RESULTS

Test of Premorbid Functioning

This test was analyzed as a method for determining whether the participants included in the study were similar between all conditions, in terms of premorbid functioning. A one-way between subjects ANOVA was conducted to compare the differences between the conditions. No significant effects were found at the $p < .05$ level for all four conditions [$F(3,95) = 1.15$, $p = .334$]. This indicates that all of the participants were similar in terms of premorbid functioning, regardless of their designated condition.

Digit Span

A one-way between subjects ANOVA was conducted to compare the effect of substance use in MCI patients on the Digit Span subtest for the conditions of Subjective Memory Loss without Substance Use, Subjective Memory Loss with Substance Use, MCI diagnosis without Substance Use, and MCI diagnosis with Substance Use conditions. A significant effect was found at the $p < .05$ level for the four conditions [$F(3,95) = 3.90$, $p = .011$]. The Bonferroni Post Hoc test indicated that the mean score for the Subjective Memory Loss without Substance Use ($M = 89.09$, $SD = 12.81$) condition was significantly different than the MCI diagnosis without Substance Use ($M = 101.11$, $SD = 13.20$) condition, although neither the MCI diagnosis with Substance Use ($M = 88.75$, $SD = 13.30$) or the Subjective Memory Loss without Substance Use ($M = 96.32$, $SD = 13.72$) conditions differed significantly from any of the other 3 conditions (Table 1).

Trail Making A

The ANOVA revealed no significant differences at the $p < .05$ level between any of the conditions for the Trail Making A test [$F(3,95) = 1.35, p = .263$] (Table 1).

Trail Making B

The ANOVA revealed a significant difference between the conditions at the $p < .05$ level for the Trail Making B test [$F(3,95) = 2.87, p = .040$]. The Bonferroni analysis revealed that the significance was found between the MCI diagnosis with Substance Use condition ($M = 80.13, SD = 10.84$) and the Subjective Memory Loss without Substance Use condition ($M = 96.62, SD = 15.26$). The Subjective Memory Loss with Substance Use ($M = 89.91, SD = 18.78$) and the MCI diagnosis without Substance Use ($M = 95.37, SD = 15.28$) conditions both had insignificantly different mean scores compared to the other conditions (Table 1).

Controlled Oral Word Association Test

The ANOVA revealed a significant difference between the conditions at the $p < .05$ level for the COWAT as well [$F(3,95) = 5.32, p = .002$]. The Bonferroni analysis indicated significance between the MCI diagnosis with Substance Use condition ($M = 80.25, SD = 13.02$) and both the MCI diagnosis without Substance Use ($M = 98.37, SD = 13.32$) and the Subjective Memory Loss without Substance Use ($M = 96.79, SD = 14.18$) conditions. The Subjective Memory Loss with Substance Use condition ($M = 88.11, SD = 11.80$) was not significantly different than any of the other conditions (Table 1).

Table 1. Mean scores for each assessment included in the study. Data are divided by the mean score of individuals within each condition.

Mean Assessment Scores by Condition				
Assessment	Subjective Memory Loss without Substance Use	Subjective Memory Loss with Substance Use	MCI diagnosis without Substance Use	MCI diagnosis with Substance Use
Digit Span	96.32	89.09	101.11	88.75
Trail Making A	97.35	97.96	99.16	88.63
Trail Making B	96.618	89.91	95.37	80.13
COWAT	96.79	88.11	98.37	80.25

DISCUSSION

The initial hypothesis was that individuals in the MCI diagnosis with Substance Use condition would have significantly lower scores on the assessments than any of the other conditions. This would have suggested a possible combined effect on executive functioning related to two conditions shown to impair executive functioning, Mild Cognitive Impairment and Substance Abuse. For all of the assessments in our analysis, the MCI diagnosis with Substance Use condition had the lowest mean score. This indicates that substance abuse history, when comorbid with a diagnosis of MCI, appears to be related to an overall effect on executive function. The hypothesis was only partially supported, as some differences did not meet the pre-determined significance level and the associated effect sizes were small.

For the MCI diagnosis with Substance Use group, the Trail Making B test and the COWAT scores were significantly lower than some of the other condition groups. On Trail Making B, the Subjective Memory Loss without Substance Use condition had a much higher score. Because the MCI diagnosis with Substance Use group had both substance use and mild cognitive impairment while the Subjective Memory Loss without Substance Use group had neither, this was expected. The MCI diagnosis with Substance Use condition on the COWAT showed significance from the Subjective Memory Loss without Substance Use condition as well, but also showed a significant difference from the MCI diagnosis without Substance Use condition. This indicates that the addition of substance use was associated with significantly different scores on this assessment when a diagnosis of MCI was involved.

Results from the MCI diagnosis without Substance Use and the Subjective Memory Loss with Substance Use groups were informative. These groups were examined together because

each condition included one of the variables of interest. In the data from all four of the assessments, individuals with a history of substance use but no MCI diagnosis received lower scores than those with an MCI diagnosis but no substance use history. These differences were not significant for any of the tests except Digit Span. With a larger sample and similar results, however, the data would suggest substance abuse was associated with significant impairment comparable to that associated with MCI.

The Subjective Memory loss without Substance Use condition produced scores that were atypical. Even though these participants should have exhibited the highest set of scores, since they were the only group who were not subject to either of the impairing variables, this was only the case for the Trail Making B test. In all of the other assessments, this score was actually lower than the MCI diagnosis without Substance Use condition, although none of the differences between any of the tests were significant. This indicates that the individuals without a diagnosis of MCI actually exhibited a higher level of ‘impairment’ than those with a diagnosis of MCI, although if this was the case, there must be other underlying conditions that were not measured causing impairment, since they were not subject to either of the variables that we measured which cause impairment.

Limitations

There were a number of limitations with the present study. The limited number of individuals in the Subjective Memory Loss with Substance Use condition and MCI diagnosis with Substance Use condition resulted in low power for the analyses. A larger sample for all the groups would provide sufficient power for analysis. It is important to note, however, that significant effects were found between some of the conditions examined even with low power. It

is likely that with higher power in analysis, greater significance between the conditions would be found.

Another potential limitation was the variability in symptomology across patients. Due to the nature of the records reviewed, which utilized different terminology by different clinicians, the criteria for inclusion in each condition was not as specific as would be ideal. Substance abuse history was not documented thoroughly, only noted whether it was “significant” and the primary drug of choice was identified. A diagnosis of MCI was also variously determined. While all diagnoses were clinically indicative of progression risk to Alzheimer’s Dementia (AD), they were termed in different manners, such as MCI vs. Early Alzheimer’s or MCI, likely of an Alzheimer’s variety, among other terms. This created uncertainty about how likely each specific diagnosis was for progression to AD. This limitation could be addressed in future studies by utilizing consistent diagnostic and inclusion criteria.

Another limitation relates to the instruments included in the initial clinical assessment. Although validated as measures of executive function, they each measure different sub-domains. Those sub-domains may be differentially affected by specific substances, resulting in some assessments sensitive to impairments some individuals experience but not others. Furthermore, the tests included in this analysis do not provide a comprehensive assessment of executive functioning. Future research would focus on specific domains within executive function, or the specific impairments caused by substances, as a way to verify that they are the same ones affected by AD, and actually exhibit a synergistic effect.

Applications

Taking into consideration the previously mentioned limitations regarding generalizing the results of this study, specifically with the inadequate sample size, there may be several applications for the results. Even though the differences between the conditions were generally not significant, the MCI diagnosis with Substance Use group did have the lowest scores for all of the tests measured. This indicates that there may be a cumulative effect between substance use and mild cognitive impairment on executive function deficits. Further research employing more stringent criteria and a greater number of participants is needed, but if this trend is supported, the implications are far reaching. With the current trend of demographics in the U.S., there may soon be many more cases of individuals who are positive for both MCI as well as a history of substance abuse. This could help clinicians to understand the nature of probable AD much sooner based upon known history of the individual. Treatment could be developed in a more individual manner, and diagnoses could be utilized with more certainty. Furthermore, more research could be directed toward discerning specific deficits from certain substances, and help understand how each substance affects the course of MCI diagnosis. Beyond knowing more about the effects of both of these disorders, the knowledge gleaned from discerning any cumulative effects could lead the way to understanding what interventions might be utilized for reducing or repairing deficits caused by substance abuse.

Summary

Substance abuse is problematic, simply put. Overdose rates are at all-time highs. Trends show multiple statistics on the rise associated with use and complications related to use. Furthermore, substance use has been shown to affect certain domains within executive function.

These impairments are exacerbated when substance abuse is comorbid with specific other disorders that are also known to affect executive function. One disorder known to affect executive functioning, but which has not to our knowledge been examined within the context of substance abuse, is Alzheimer's Dementia (AD), or Mild Cognitive Impairment with a clinically indicated risk of progression to AD. This study sought to address that by comparing groups subject to each of these disorders exclusively, a group subject to none of them, and a group subject to both of them, using a variety of tests that have been validated for measuring executive function.

These tests were compared using a between subjects one-way analysis of variance. Although a Bonferroni post hoc analysis revealed that the condition of participants with both an MCI diagnosis and substance use history did receive lower average scores than the other conditions across all of the tests, most of the different condition scores between the tests were not significant. Some of the tests had differing conditions with significance, none of them exhibited significant differences between the MCI diagnosis with Substance Use condition and the rest of the conditions measured. We discussed limitations, which included our small sample size. Even so, the trend discovered may be promising, pending further research supporting the same conclusions. We discussed applications of the findings, including better understanding and being able to better individualize treatment for patients who have a history of substance use when considering a diagnosis of mild cognitive impairment or Alzheimer's Disease.

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APPENDIX



Missouri State UNIVERSITY

To:

Steven Capps
Learning Diagnostic Clinic, Psychology
William Deal

RE: Notice of IRB Approval

Submission Type: Initial

Study#: IRB-FY2018-756

Study Title: Executive Functioning Impairments for Dementia Patients With or Without Substance Use History **Decision:** Approved

Approval Date: March 18, 2019

Expiration Date: March 17, 2020

This submission has been approved by the Missouri State University Institutional Review Board (IRB) for the period indicated.

Federal regulations require that all research be reviewed at least annually. It is the Principal Investigator's responsibility to submit for renewal and obtain approval before the expiration date. You may not continue any research activity beyond the expiration date without IRB approval. Failure to receive approval for continuation before the expiration date will result in automatic termination of the approval for this study on the expiration date.

You are required to obtain IRB approval for any changes to any aspect of this study before they can be implemented. Should any adverse event or unanticipated problem involving risks to subjects or others occur it must be reported immediately to the IRB.

This study was reviewed in accordance with federal regulations governing human subjects research, including those found at 45 CFR 46 (Common Rule), 45 CFR 164 (HIPAA), 21 CFR 50 & 56 (FDA), and 40 CFR 26 (EPA), where applicable.

Researchers Associated with this Project:

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