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Visual Attention, Color Processing and Physiological Measure Differences in Males and Females with Substance Abuse and Opiate Addiction

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ABSTRACT

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A biological marker of the addictive state would be a major breakthrough in objectively assessing the efficacy of treatment outcomes. Given its role in the mesolimbic system and drug reward, most biological marker studies for addiction focus on measures related to dopamine (DA). Dopamine is also implicated in some disorders of visual attention and plays a modulatory role in the processing of color in the retinal DA pathway. For example, visual processing in the retina has been shown to co-vary with DA levels during cocaine withdrawal.

In this electroencephalographic (EEG) study, we studied event related potentials (ERPs) and reaction time (RT) in opiate addicts—recruited from a community-based high intensity residential substance abuse and detoxification treatment program—and their age- and gender-matched controls. Using a visual color recognition Go/NoGo task with three similar blocks, participants responded in each block to a "Relevant" stimulus of one of three randomly-presented Red, Green or Blue light stimuli as instructed, while ignoring the other two "Irrelevant" stimuli. This simple task produced robust ERPs that were well-differentiated in the visual evoked potentials (VEPs) obtained by the Relevant stimulus compared to the VEPs from Irrelevant distractor stimuli. P300 ERP amplitudes from the color recognition task were significantly higher in males than females. Similar results were obtained with the frontal late positive (LP) potentials (i.e., 700 msec after stimulus onset), which occurred 200-300 msec after the average participant response/ RT.

While there were no significant RT differences between controls and addicts in the task, male controls had significantly greater P300 and LP potentials than female controls, suggesting sex differences in visual color processing. However, there were also significant differences in P300 amplitudes male controls and addiction participants—suggesting a difference in retinal DA production in opiate addiction. Further to the hypothesis of sex differences in visual color processing, P300s and LPs were not significantly different in female controls compared to female addicts. Changing the color wavelength of the Relevant stimulus did not significantly affect ERPs in males or females, controls or addicts at P300 but did at LP, particularly when the color blue was relevant. These findings suggest that there are significant sex differences in retinal DA production for opiate addicts and controls in visual processing for a simple Go/NoGo color recognition task.

Keywords: EEG, visual attention, opiate addiction, sex differences, substance abuse, color processing, ERP, VEP

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CHAPTER 1

Introduction

Addiction is a chronically relapsing disorder (O'Brien, 1996), which often begins with recreational use and deteriorates into obsessive drug taking and drug seeking (DiFranza, 2008). Partly through the urging of the National Institute on Drug Abuse (NIDA) (see Leshner, 2000), and partly due to the lack of evidence that traditional addiction treatment programs work in stopping drug seeking behavior (Hoffman & Froemke, 2007), over a decade of research interest has been directed more recently toward the *process* of addiction. Many addiction research labs are now examining the 'neuroadaptations' which correlate with changes in substance abuse (Everitt & Wolf, 2002; Nestler, 2001; White & Kalivas, 1998).

Need for Identifying Biological Markers in Addiction

In a meta-analysis of the literature on biological markers of cocaine addiction, Elkashef and Vocci (2003) posited that the discovery of a reliable biological marker or trait for addiction would be a major breakthrough. State markers would be extremely helpful if they change consistently in relation to the drug dependency state distinguishing acute vs chronic effects, or in the abstinence state distinguishing between acute withdrawal and the more prolonged craving state with further relapse. An important component for any therapeutic individual multimodal addiction treatment plan would then be to identify specific biological changes that could be used to monitor and tailor treatment objectively (Hyman, Malenka, & Nestler, 2006).

In addition, a reliable biological marker of addiction might be helpful for: 1) Targeting specific pharmacological agents for subgroups of addicts; 2) Determining the length of treatment evidenced to be beneficial; 3) Preventing relapse by initiating treatment at the earliest sign of an

increase or re-emergence of a certain marker; and 4) Understanding traits that might predict or indicate high risk for opioid use, misuse, dependence, and addiction.

Opiate addiction biomarkers. The origins of aberrant behavior in opiate use are not always similar, including for long-term synthetic or partial synthetic opiate or 'opioid' therapy for chronic pain associated with prescription pain pill abuse and addiction (Passik, 2009). With such diversity in high risk or predisposition for opioid dependence and addiction there is great need for thorough, individualized, ongoing assessment of those with problematic opiate and prescription opioid abuse necessitating a multimodal therapeutic plan fashioned from cognitive, behavioral, and interventional techniques; one that gives evidence that the treatment allows for male and female differences in substance abuse and addiction. (Please note that as the psychopharmacological properties of opiates and opioids have the same neuropsychological and neurobiological outcomes particular to the literature of this study both terms are used throughout as research studies indicate and should not be considered two different substances in this context).

Traditionally there has been little discussion or research regarding the implications of sex differences in the neural substrates that may ameliorate the effects of certain drugs for males as opposed to females, including opiate/opioid use (Back et al., 2011; Hamilton & Grella, 2009). However, in a recent study of almost 30,000 assessments from 220 treatment centers across the United States, Green, Grimes Serrano, Licari, Budman, and Butler (2009) found that women were more likely than men to report any prescription opioid use for pain problems but not for other medical problems; women also reported more abuse of prescription opioids in the past month. The same report found that this abuse correlated more for women with alcohol problems

than men and with inhalant use and a history of drug overdose while men's opioid abuse correlated more with living with their children, hallucinogen use, and recent depression.

Electroencephalographic (EEG) Study of Abnormal Cognition

Non-invasive electrophysiological scalp recordings, such as event-related potentials (ERP) and visual event potentials (VEP) are recognized as an objective technique for studying neuronal information processing associated with normal and abnormal cognition (Chiappa, 1997; Luck, 2005) including those found in long term drug use. For example, P300 assessment of detoxification effects on cognition in opiate and cocaine users are meliorated by buprenorphine (Kouri, Lukas, & Mendelson, 1996), while the N100 is believed to reflect changes in selective attention in that N100 amplitudes increase when directed attention toward task-relevant stimuli increases (Hillyard & Picton, 1987). Little is known regarding the functional significance of the visual ERP component called the late positive (LP) potential, other than the emotional intensity of a stimulus affects it—either positive or negative stimuli elicits a larger or more positive LP than neutral stimuli. The LP is most pronounced around 400-600 ms following the VEP but can last up to a second past the stimulus. Recently Brown, van Steenbergen, Band, de Rover and Nieuwenhuis (2012) reported some evidence of decreased N100 and P100 amplitudes that accompanied large LPs elicited by unpleasant visual stimuli (i.e., spider pictures), this observation may indicate the LP reflects a global inhibition of activity in the visual cortex.

Event related potentials (ERPs) in a Go/NoGo visual paradigm. The current study extended the results of visual object recognition tasks used in previous studies (Nash, 2009; Steffensen, Ohran, et al., 2008; Wolf, 2011) to determine if there were also significant gender differences in a color recognition task. Participants completed a new color visual processing task where the visual stimuli consisted of three randomly-presented screens of one solid-color each.

A blue screen flash served as the target *Relevant* stimulus; while red and green screens served as *Irrelevant* stimuli. The Relevant and Irrelevant stimuli appeared randomly during each of the EEG sessions. Participants were instructed to press a key pad button when the Relevant stimulus was randomly presented, but to not respond when the Irrelevant stimuli were presented.

The current study seeks to better understand and extend any neuronal sex differences in opiate addiction using a cognitive neurophysiological electroencephalogram (EEG) study (Bauer, 2001; Luck, 2005). The potential benefit that may accrue to society include insight into biological markers of addiction and their utility as an adjunct to objectively monitor treatment outcomes of addiction. Understanding the unique differences women and men face in addiction, treatment, and recovery that may be due to distinctive differences physiology, hormones, mental health, and/or life circumstance is very important (Back, et al., 2011; Green, et al., 2009) and would allow for appropriate and specific therapy tailored to gender differences in drug use or abuse experiences, speed of addiction progression, or differences in triggers for relapse that would affect rehabilitation and recovery maintenance.

The main objective of this study was to evaluate select behavioral, physiological and molecular markers in male and female opiate abusers as seen through electrophysiological scalp readings or their utility as objective indices of the addictive state. The primary hypothesis is that visual processing, in particular blue color vision, differs significantly between males and females, and that blue color processing, which is regulated by the neurotransmitter dopamine (DA) in the retina, and reflects DA neurotransmission in the mesolimbic system implicated in drug and natural reward, can be exploited as a biological marker of the addictive state. Thus, a biological marker might provide an objective index for the efficacy of treatment strategies for addiction, in particular opiate addiction. Specifically, can we objectively measure improvement,

either physiologically and/or behaviorally in opiate addicts by measuring DA neurotransmission through evaluation of blue color processing in the visual system?

This study investigates how substance abusers and addicted participants visually process color information, using electroencephalography (EEG) to measure VEP latencies and amplitudes, in particular the P300 and the P700 or late positive (LP), of males versus females substance abusers and addicts—particularly opiate addicts.

CHAPTER 2

Review of Literature

Drug misuse and abuse are major social, legal, and public-health problems as evidenced in three main categories: long-term individual physical harm caused by the drug (i.e., damage to organs and systems); induced drug dependence; and the societal effect on families, communities, legal systems and nations (Nutt, King, Saulsbury, & Blakemore, 2007). Throughout the world increased efforts are being taken to develop improved and more appropriate, individualized methods of assessment and proven rehabilitation- and reintegration-oriented treatment strategies that prove to effectively respond to drug use disorders and their consequences.

Prevalence of Substance Abuse and Opiate Addiction

Illicit and legal substance abuse and addiction are worldwide and in general take an enormous toll in individual human suffering (Rehm et al., 2009), with the prevalent misuse of synthetic opioids and other prescription drugs recognized as a growing health problem in a number of developed and developing countries. In 2010, the World Health Organization (WHO) estimated that each year 155 to 250 million people of the world's population ages 15-64 regularly (past month) use illicit drugs (i.e., cannabis, amphetamines, cocaine, opioids, and non-prescribed psychoactive prescription medications (United Nations Office on Drugs and Crime, 2010), causing a significant global social burden from health and disease problems. In Africa, Asia, Europe and Oceania, nearly half of the reported drug-related deaths were attributed to opioid fatal overdoses, while in the Americas it was cocaine. However, it should be noted that in a study of case histories using buprenorphine treatment (a partial agonist at the mu opioid

receptor) for prescription opioid addiction, Mendelson, Flower, Pletcher, and Galloway (2008) reported that prescription opioid drug addiction was a major health problem of epidemic proportions—one that exceeded cocaine use in young people in the United States.

The economic and societal implications arising as direct or indirect results of either substance abuse or addiction are staggering with consequences arising from lost job productivity, squandered earnings, rising healthcare costs, costs related to criminal activity, incarcerations, investigations, vehicular accidents, domestic and non-domestic violence, risky sexual behaviors, HIV or AIDS infection, premature births and deaths, and to the breakdown of the family unit.

Current Conditions in Cognitive Assessment in Substance Abuse and Addiction

The need for improved evidence-based methods of assessment and individualized treatment of addiction arising from substance abuse are also being requested by workers in medical and mental health fields alike particularly in cognitive outcomes. For two decades the *Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV)*; The American Psychiatric Association (APA; 1994) has recognized substance abuse and substance dependence or addiction as two separate mental disorders—(See Appendix A for DSM-IV current criteria and suggested DSM-V revisions for May 2013 implementation)—suggesting biological differences in the cognitive and behavioral consequences from different types of substance abuse or addictions. This categorization for assessment and diagnostic purposes was based on the Alcohol Dependence Syndrome, a construct that represented impaired control of drinking that was generalized to other drugs and substances of abuse by the World Health Organization in 1981.

It is currently being proposed by the APA to retitle the category *Addiction and Related Disorders* to account for physician confusion in diagnostic criteria labels of "dependence" versus

"addiction" regarding patients needing long-term chronic pain opioid pain medication and fear of clients being labeled "addicts" because of the withdrawal symptoms associated with "tolerance" development in long-term use. Accordingly, the word "dependence" is now limited to physiological dependence, which is considered by some a normal response to repeated doses of many medications including beta-blockers, antidepressants, opioids, anti-anxiety agents and other drugs (see American Psychiatric Association, 2012), reaffirming the need to be able to biologically and neurophysiologically assess any cognitive changes arising from substance abuse.

Problems identified by the American Psychiatric Association in combining substance abuse and dependence into one disorder for the upcoming *DSM-V* have led to many worldwide/cross cultural studies of the biological and neurophysiological structures of the abuse and dependence in a variety of general population and clinical settings. Given the empirical evidence from these studies, the DSM-V Substance Use Disorders Workgroup recommends combining abuse and dependence into a single disorder of graded clinical severity, with two criteria required to make a diagnosis; another indication for more evidence-based neurophysiological and biological based tools of assessment are needed to couple with any traditional psychological assessment during the different stages of rehabilitation and recovery from addiction.

Need for Evidence-Based Neurobiological Assessment of Substance Abuse Effects on Cognition

Many have suggested the need for development of a universally recognized accurate way to assess the cognitive harms of various drugs when misused or abused (Porjesz & Li, 2007; Porjesz & Rangaswamy, 2007; Rehm, et al., 2009; Wolfe, 2003); one that is practical,

transparent and has a systematic framework and could be used nationally and internationally to assess the harm of current and future drugs of abuse (Nutt, et al., 2007). Currently drugs are categorized into five areas by the Food and Drug Administration (FDA) by their purported harms and risks (see National Institute on Drug Abuse [NIDA], 2011): Schedule I and II drugs have a high potential for abuse and require greater storage security and have a quota on manufacturing, among other restrictions. Schedule I drugs are available for research only and have no approved medical use; Schedule II drugs are available only by prescription (unrefillable) and require a form for ordering. Schedule III and IV drugs are available by prescription, may have five refills in 6 months, and may be ordered orally. Some Schedule V drugs are available over the counter. (For a chart of commonly abused drugs and their effects see National Institute on Drug Abuse [NIDA], 2011).

In 2000 the U.S.A. National Institute on Alcohol Abuse and Alcoholism's (NIAAA) 10th Special Report on Alcohol and Health to Congress stated there were at least 15.3 million people in the U.S. that met the criteria for alcohol abuse or addiction (Shalala, Kirschstein, & Gordis, 2000) and that the direct costs related to alcohol abuse alone ranged as high as $184.6 billion per year in the U.S.. They also reported this was an estimated 25% increase from the reported economic costs of alcohol abuse and/or alcoholism in 1992.

Within these parameters, by the year 2006 the NSDUH reported that an estimated 20.4 million Americans aged 12 or older (8.3 percent) had used an illicit drug during the month prior to the survey interview and indicated that *such* drug use had remained somewhat stable since the 2002 report for all but one of the nine illicit drug categories listed above—heroin (an opiate).

In addition to alcohol abuse reports, the Substance Abuse and Mental Health Services Administration (SAMHSA) of the United States Department of Health and Human Services

annually reports from The National Survey on Drug Use and Health (NSDUH) information on nine categories of *illicit* drug use: *Marijuana*, *cocaine*, *heroin*, *hallucinogens*, *inhalants* and the *nonmedical* use of *legal prescription-type "psychotherapeutic" namely pain relievers*, *tranquilizers*, *stimulants*, and *sedatives.*[1]

By 2010 NSDUH reported 22.6 million Americans aged 12 or older (almost 9% of the population) were current illicit drug users(used in past month), with an estimated 7.0 million (2.7 %) persons aged 12 or older reporting nonmedical use of prescription-type *psychotherapeutic* drugs and pain relievers (National Institute on Drug Abuse [NIDA], 2011; SAMHSA, 2010). (It should be noted that use of over-the-counter drugs and legitimate use of prescription drugs were not included in the study and that any data from the use of alcohol and tobacco products by those who are underage youth are not included in the national surveys' estimates.) This report also indicated that nonmedical use of prescription drugs among youths (12-17 years) and young adults (18-25 years) in 2010 had almost doubled since 2002 and was now the second most prevalent illicit drug use category (with marijuana being first). This misuse of prescription-type pain opioids has sent the costs related to *illegal* substance abuse skyrocketing to nearly $1 trillion (see Califan Jr., 2007; Hays, Ebbert, & Sood, 2009). It was this nationwide increase in opiate/opioid use and how it manifested itself in Utah that was of particular interest for the current study.

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[1] Hashish is included with marijuana, and crack is a form of cocaine. Several drugs are grouped under the hallucinogens category, including LSD, PCP, peyote, mescaline, mushrooms, and "Ecstasy" or 3,4 methylenedioxymethamphetamine (MDMA). Inhalants include a variety of substances, such as nitrous oxide, amyl nitrite, cleaning fluids, gasoline, spray paint, other aerosol sprays, and glue. The combined four categories of prescription-type drugs referred to in the NSDUH as "psychotherapeutics" cover numerous pharmaceutical drugs available by prescription and any drugs within these groupings that may be manufactured illegally, such as the stimulant methamphetamine. Respondents to the NSDUH were asked to report only "non-medical" use of psychotherapeutics, defined as use without an individual's own prescription or simply for the experience or feeling the drugs caused. For a list of commonly abused prescription drugs, including depressants, opioids and morphine derivatives, and stimulants with common/street names, methods of administration, and potential health effects see the NIDA's Revised October 2011 Commonly Abused Prescription Drugs Chart (National Institute on Drug Abuse [NIDA], 2011).

Utah Prevalence of Substance Abuse and Addiction

Utah's rate of substance abuse is somewhat different than the rest of the USA, in that it has a lower rate of tobacco and alcohol use. However, in the 2007 Utah state's Division of Substance Abuse and Mental Health (DSAMH) Annual Report (Utah Division of Substance Abuse and Mental Health, 2007), marijuana continued to be the primary drug of abuse for clients under 18, methamphetamine for clients 18-34, alcohol tied with methamphetamine use for those 35-44 with alcohol remaining the primary drug of choice for individuals over 44. In 2007, Heroin and cocaine use in Utah was similar to national statistics and had remained fairly constant over the preceding 10 years; but for various reasons heroin use spiked up in 2008 (Duda, 2008). While combined opiate (narcotic) abuse appeared to be increasing over the years 2003-2007; heroin ranked fourth behind alcohol, cocaine and marijuana in 2007 as the primary substance of abuse in clients admitted to public treatment centers. Total opiate abuse (i.e., heroin, other opiates, oxycodones, opioids, etc.) in 2007 accounted for 15.3% of overall substance abuse in male clients and 18.1% in female clients, such statistics indicated a need for research in opiate abuse particularly in Utah since this abuse was followed by an increase in crime related to substance abuse and addiction necessitating the implementation of Drug Courts (Utah Division of Substance Abuse and Mental Health, 2008).

According to the 2007 Utah Department of Human Services: Substance Abuse Services Report, the majority of crimes committed in Utah were linked to substance abuse with 70% of inmates having drug use problems and 71% of individuals discharged from treatment reporting no use, or at least a significant reduction in drug use, 30 days post discharge from jail. It was also reported in 2007 that 11% of the clients in Drug Court used heroin as the primary drug of choice. Irrespective of this news, by October 2008 (Stryker, 2008) it was reported that in Utah

prescription drugs had killed more people than car accidents with 6.5 % using prescription painkillers (most are opiate based thus called *opioids*) for nonmedical reasons; 1 in 7 users were between the ages of 18 and 25 and public education campaigns were funded by Utah's Governor's office in an effort to address the looming prescription pain killer drug abuse problems. In 2008, it was determined that the cost of helping first time offenders was too great (Israelsen-Hartley, 2008) and research from other states showed that, "…Drug Courts should serve high risk, high-need individuals—that's where the model is effective" (p. A6). Drug court costs were $4,500.00 per year as opposed to incarceration costs of $27,000.00 per year but individual help cost the State less if the first-timers were remanded to treatment.

By November 2011 the Annual Report to the Utah Legislature by the Drug Court/Drug Board Program noted that 40 Drug Courts were operating statewide in Utah (an increase from 32 in 2009) including Adult Felony, Juvenile, Misdemeanor, and Family Dependency Drug Courts in an effort to treat those struggling with drug addiction in the state and committing crimes. These courts offer non-violent drug-abusing offenders with intensive, court-supervised drug treatment as an alternative to jail or prison at a cost of $3,718,300.00 (Utah Division of Substance Abuse and Mental Health, 2011a). Unfortunately in 2011, in a cohort of 13,000 drug court participants, it was reported that 22% of the clients in Drug Court used heroin as the primary drug of choice—double the use reported in 2007—with many reporting that their heroin drug use coming from the high cost associated with an addiction to opioid pain pills. In addition, the Utah Division of Substance Abuse and Mental Health's Annual Report (2011) once more stated that "...in 2010 more individuals died from prescription drug overdose (236) than died in car accidents (235)..." (p.52) with opioids or other opiates/synthetics (Oxycodone/Hydrocodone) being the most commonly abused prescription drugs in Utah.

The history of opiates/opioids being prescribed as pain killers, with their high risk addictive properties, is long and convoluted (Berridge, 2009; Carise et al., 2007; Chou, Ballantyne, Fanciullo, Fine, & Miaskowski, 2009). The use of prescription opioids for treatment of chronic non-cancer pain has become highly prevalent yet highly controversial due to the potential harm associated with long term use including drug misuse, abuse, addiction and diversion very little in known about the long-term benefits and harms of opioids (Passik, 2009).

While treatment for chronic pain with opioid medication is considered appropriate therapy for pain related to cancer and other terminal illnesses (Du Pen et al., 1999), recent studies give evidence for reasons for further evidenced-based research in the safety and long-term efficacy of similar opioid therapy for chronic noncancer pain because of their highly addictive qualities (Chou, et al., 2009; Turk, Swanson, & Gatchel, 2008; Webster & Webster, 2005). Indeed, as of June 1, 2010, forty-two states including Utah are actively applying legislated regulations for required physician involvement in on-line prescription drug monitoring systems and continuing education in the addictive properties of opioids before relicensing if able to prescribe Scheduled drugs for treatment of pain (Kentucky All Schedule Prescription Electronic Reporting Program [KASPER] Evaluation Team, 2010; National Alliance for Model State Drug Laws Official Site, 2009, August). Unfortunately, as of November 2011, there are over 88,251 adults in Utah who need substance abuse treatment—while only 14,934 treatment slots are available (both privately and publicly) and over 12,189 Utah youth need substance abuse treatment—while only 1,520 slots are available (Utah Division of Substance Abuse and Mental Health, 2011).

With such high rates of any substance abuse and/or opiate addiction world-wide and the obvious lack of evidence-based assessment and treatment programs available, there is need for

further research for less costly ways of recognizing the biological and neurophysiological risk factors for the disinhibition that accompanies substance abuse or addiction; ones that correlate with currently used self-report methods for addiction severity such as the Addiction Severity Index, Fifth Edition (ASI-5) for being at risk for increased cravings and relapse (Back, et al., 2011; Green, et al., 2009; Murphy, Hser, Huang, Brecht, & Herbeck, 2010).

It is well known that the risk of possible relapse increases as clients indicate drug craving increases while seemingly inhibitory responses decrease, especially for those who are in treatment or have undergone treatment and are trying to maintain their recovery (Biederman & Vessel, 2006; Bloom, 1993; DiFranza, 2008; Field & Cox, 2008; Hays, et al., 2009; Hyman, et al., 2006; Kalivas & Volkow, 2005). Relapse does not occur spontaneously; more often over a period of time therefore a cost efficient method that recognizes neurobiological decreases in recognized inhibitory responses following drug use and when in withdrawal or extended abstinence from the drug would be helpful in improving treatment outcomes.

Research has recognized biological markers of opiate addiction as relevant today given the availability of such substances (legal and illegal), including changes in neurotransmitter systems especially those that effect the mesolimbic DA system (Anton & Leff, 2006; Charles et al., 2003; Coviello, Alterman, Cacciola, Rutherford, & Zanis, 2004; Gonzalez, Oliveto, & Kosten, 2004; Grinenko, Krupitskii, & Zvartau, 2003; Rich et al., 2005; Yao et al., 2006), and help to run the risk of pleasure seeking through opiate addiction acquired from either long-term illicit or prescribed use.

Mesolimbic Dopamine (DA) System Implicated in Opiate Addiction

Animal studies involving intravenous self-administration of drugs of abuse have identified neural substrates that mediate the reinforcing actions of opiates (Sim-Selley, Selley,

Vogt, Childers, & Martin, 2000). Opiates are primarily central nervous system (CNS) depressants and narcotic analgesics that come from opium which contains phemanthrene alkaloids that are highly addictive and controlled by law—both nationally and internationally. From these alkaloids come morphine, codeine, and thebaine—the natural opiates (Alphatect, 2009). The regions these drugs affect constitute part of the brain reward system that has evolved for mediating natural motivated behaviors—the mesocorticolimbic dopamine (DA) system originating in the ventral tegmental area (VTA) of the midbrain (Bloom, 1993; Kalivas, Churchill, & Klitenick, 1993; Koob, 1992; Schultz, Dayan, & Montague, 1997). The VTA system is implicated in the habit-forming actions of several addictive drugs (for recent review see Wise, 2004). The dogma is that any drug or behavior that increases VTA DA neuron activity will be rewarding and potentially addictive (Kalivas, et al., 1993; Kalivas & Volkow, 2005; Nestler, 2001). However, the neurobiology of the addiction process involves multiple neural circuits (Diana et al., 2008; Jackson et al., 2009; Olsson et al., 2009; Steffensen, Taylor, et al., 2008; 2009) and any analyses of quantitative biological and neurophysiological data is important for understanding these heterogeneous and complex disorders.

Treatments for addiction. The search for effective medications for substance abuse and addiction has been somewhat elusive (Anton et al., 2008; Biederman & Vessel, 2006; Coviello, et al., 2004; Gonzalez, et al., 2004; Rich, et al., 2005). It is believed that poor results are because of the neuroleptics often used in addiction treatment (major tranquilizers and antipsychotic drugs that reduce confusion, delusions, hallucinations, and psychomotor agitation in patients with psychoses). These target the mesolimbic DA system, produce akinesia and disrupt natural pleasure sensations, resulting in lack of compliance in patients (Kalivas & Volkow, 2005; Yue,

Vessel, & Biederman, 2007) and in particular for heroin addiction and treatment (Lubman et al., 2009).

Opiate addiction treatment. Regarding opiate addiction, ever since the landmark studies of Dole and Nyswander (1965), methadone has been the mainstay of the medical treatment in opiate addicts for whom detoxification and a drug-free lifestyle have been unsuccessful (Fishbein et al., 2007; Gonzalez, et al., 2004). Indeed, the success of agonist replacement therapy, first with methadone, and more recently with the partial agonist buprenorphine (e.g., Suboxone®), have elevated agonist replacement therapy as a standard of care for the treatment of drug and other chemical addictions—both legal and illegal (Back, et al., 2011; Gonzalez, et al., 2004; Gordon et al., 2010; Kouri, et al., 1996; Mendelson, et al., 2008). However, there is increasing concern in the society about the failure of substitution therapies to lead to a long-term, stable drug-free lifestyle (Fischer, Jenkins, Bloor, Neale, & Berney, 2007; Lubman, et al., 2009). For clinical purposes, there are few alternatives for the patients whom have lifestyle and health issues or legal constraints related to opiate addiction that make medical assistance mandatory (Dole & Nyswander, 1965; Gonzalez, et al., 2004).

Biological Markers of Addiction

Perhaps the failure to discover how such medications work is due to inadequate understanding of the underlying biology in the pre-morbid condition and subsequent lack of recognition of the neuroadaptations that accompany substance misuse and abuse (see Elkashef & Vocci, 2003; Porjesz & Li, 2007). Population heterogeneity could be a major factor in the poor response to medications (Hyman, et al., 2006; Porjesz & Rangaswamy, 2007). Thus, identifying specific biological markers and/or traits in addicts is essential for developing effective treatment strategies for addiction. In a review of the literature, Elkashef and Vocci (2003) found that most

of the studies addressing biological markers of addiction focused on measures related to DA. Their meta-analysis found that serum prolactin levels as indicated by electroencephalographic (EEG), positron emission tomography (PET), and electroretinogram (ERG) are the most promising biological markers of addiction, in particular for or in cocaine addiction, which is the focus of most studies to date, given its well-known DA facilitatory effect. For example, 40-60% of chronic cocaine users had evidence for low DA tone as evidenced by increased prolactin, decreased b-wave (DA-dependent component of the ERG), and decreased DA D2 receptor occupancy and DA release on PET scans. These measures could be useful tools to screen participants for their DA tone.

Electrophysiological Responses: Visually-evoked Potentials and Event-related Potentials

Event-related potentials (ERPs). Since the first published paper on human electroencephalogram (EEG) in 1929 by the German neurologist and psychiatrist Hans Berger reporting measured electrical activity off of the cranium, this neurophysiological measure has been used to try and better understand mental processes in humans. EEG revolutionized daily neurologic and neurosurgical procedures from 1930-1970 (Tudor, Tudor, & Tudor, 2005). The study of evoked potentials, namely visually-evoked potentials (VEPs) and auditory-evoked potentials (AEPs) became indispensable in clinical practice for neurosurgeons especially in understanding seizures until computed tomography (CT) was invented. It continues to be important today especially when paired with other gross pixel neuroimaging for understanding seizures, brain tumors, degenerative brain changes, and other brain diseases. In particular, advances in electrical activity research investigating late occurring cortical waveform components, or event-related potentials (ERPs), are thought to represent both the functional neural activity evoked by discrete stimulus experiences, and/or by cognitive psychological

constructs related to task requirements. Table 1 gives a summary of the noninvasive neurophysiological measures recognized and used as ERPs in research looking for possible cognitive processing correlates (for more in-depth review see Handy, 2005; Luck, 2005)

Table 1

Neural and Physiological Substrates of Event-Related Potentials (ERP) and Associated Cognitive Processes

ERP Components	Electrode Sites	Polarity (+ or −)	Time (ms) (post-stimulus) Start	Peak	Associated Neural Substrates	Cognitive Processing Stimuli and Other Factors
Visual						
C1	Posterior-midline	+ and − (varies)	40-60	80-100	V1 (primary visual cortex) – enfolded in calcarine fissure (+ upper field, - lower field)	First major visual component; highly sensitive to contrast and spatial frequency. Summates with P1 if + (horizontal stimuli midline).
P100 (P1)	Lateral Occipital	+	60-90	100-130	Early – dorsal extrastriate cortex (middle occipital gyrus). Later – ventral fusiform gyrus 30 distinct areas within 100ms	Variation in stimulus parameters: contrast, spatial frequency direction, subject state of arousal.
N100 (N1)	Anterior	−	75-100	2 @ 150- 200	1. Parietal cortex 2. Lateral occipital cortex	Spatial attention; larger for discrimination than detection.
P200 (P2)	Anterior and Central	+	Follows N1		Hard to distinguish from overlapping N1, N2, P3	Larger for target and infrequent, simple stimulus.
N170 and Vertex Positive Potential	Vertex	−	150	170	Lateral occipital, right hemisphere; none in inferotemporal cortex	Attention; endogenous components.
N200 (N2)	Posterior	−	150	350	occipital	Spatially viewed *deviant* task—if task relevant; orienting reflex; breaks into 3 distinct components. [2] presents very young (1 month); discriminating, higher amplitude in

						sleep (most prominent at beginning of sleep), automatic and controlled attention; detect group differences.
N2a	Posterior	−	200	220		deviant task-irrelevant = mismatch negativity (MMN).
N2b	Posterior	−	200	220		Deviant task related; bilateral and probability sensitive - unsure if homologous to auditory N2b neural processing.
N2pc	Posterior – contralateral to location of target	−	200	220	Occipital and parietal (pc)	component seen posterior and contralateral (pc) to location of target; not probability sensitive; focus of spatial attention on target; seen in visual working memory tasks; working memory maintenance.
Auditory						
BER	Brainstem evoked response		10		Brainstem; medial geniculate nucleus; primary auditory cortex	Sound.
N1 (several sub-components)	Fronto central	−		75	Auditory cortex – dorsal surface temporal lobes; [2] contralateral supra temporal cortices; subcortical thalamocortical and reticular formation; [3]thalamus	Attention; endogenous components. [2] Early perceptual, stimulus specific, needs 30-40 stimuli presents to establish, more when odd or rare – non target; not detected in 4-5 yr olds, in parietal sites at 6-7 yrs; not reliable until 10-11yrs; MMN; [3] top down modulation to sound
	vertex-maximal potential	−		100	unknown region	Attention.
	lateral	−		150	superior temporal gyrus	Attention.

N2	Central	−	200	200-220		Stimulus categorization process; repetitive, non-target (if task-irrelevant *deviant* stimuli presented in repetitive train = N2a (mismatch negativity, MMN); if task-relevant then get N2b; orienting reflex; not sure if homologous to visual N2b neural processing. [2]present very young (1month).
Mismatch Negativity (MMN)	Central midline scalp	−	160	220	Not same in auditory versus visual.	Repetitive series of identical stimuli and infrequent mismatching ones; involuntary sensory memory trace comparison.
Visual and Auditory						
P300 (P3)	Frontal maximal	+	300	550	Not certain – no clear consensus of what neural or cognitive processes involved. [2]temporal lobectomies decrease P300; prefrontal lesions decrease AMP in fronto central; widespread neurons – hippocampi, frontal lobes, thalamus in humans; parieto-central/ centro-frontal changes with maturation	Affects AMP and LAT – AMP smaller if subject uncertain/ larger with increased difficulty; LAT increase if experiment influences processing; probability related; categorized mental task; influenced by unpredictable infrequent shift in tone pitch or intensity unexpected. [2]cognitive processing – not motivational; LAT: small decrease 4-10 yrs (550 to 474ms), significant drop 12 yrs (339 to 344ms), constant during perceptual and motor interference, increases when load increased(searching memory for more information; AMP: 10 yrs broad distributed scalp display/ adolescent sharp time phasic with

						maximum at parietal midline/ as get older to frontal—increased temporal separation smaller vertex to broader frontal position—from fronto-central to parieto-central occurs with age; high AMP reflects confidence in perceptual decision, increases if target improbable.
N400 (LN-late negative)	Central and parietal – right hemisphere	−	350	450	Left anterior medial temporal lobe (auditory)	Language specific. Response to semantics misuse in language – sentence doesn't match preceding lines.
P600 (LP-Late Positive)	Left frontal	−	300	700	Frontal cortex; left hemisphere activity dependent	Syntax of conversation, i.e., wh__? questions.
RP (Response time)	Depends on efforts used by subject	+ − +	100ms before response			Inattention – readiness potential; lateralized to the hand making the response.
LRP (lateralized response potential)	Contralateral to hand vs foot as they together work to do task	+			Motor cortex	Prepared for response; responses are faster when LRP is larger at moment of stimulus.
ERN (error related negativity)	Frontal central	−	After error made		Anterior cingulate cortex	Error detection using negative feedback from wrong response or by watching others make a mistake.
N10	Vertex potential Action potentials	− and +	10-20	20-100	Somatosensory, olfactory, and gustatory responses	These are not post-synaptic potentials but action potentials from peripheral nerves, followed by subcortical components and short and medium latency cortical components. N1 followed by P2 together are called vertex potential.

	Hard to record olfactory and gustatory ERP responses.

Note: AMP = amplitude; LAT = latency; yrs = years; N1 = N100; P1 = P100; N2 = N200; P2 = P200; P3 = P300.
[1]As summarized from Luck, S. J. (Luck, 2005).
[2]See Grant, M. L. (1993)
[3]See Frith, C. D., & Friston, K. J. (1996).

Scientists have tried different ways to measure this brain activity for over a hundred years in order to better understand perceptual, cognitive and motor functions (Näätänen, 2000; Otten & Rugg, 2005). Unfortunately, not all methods that study brain activity have been non-invasive (Gazzaniga, 2005) as researchers tried to see when, and from where, neural activity is generated. The question asked iswhether it is generated from environmental sources such as mind-altering drugs (exogenous stimuli) or internally from mental cognitive processes (endogenous stimuli), or both.

P300 in substance abuse and addiction. Particular to the current study, the P300 event-related potential (ERP) has shown to be a good measure of human cognition, providing an objective measure of brain activity that is very sensitive to any central nervous system (CNS) disruptions and pharmacologic manipulations (Polich, 2004)—including possible biological and/or genetic underlying mechanisms of brain oscillations that drive the ERPs (Begleiter & Porjesz, 2006).

For example, decreased P300 amplitudes in *acute* ethanol and marijuana use with no consistent differences in latencies has been recognized for over 35 years (Kopell, Roth, & Tinklenberg, 1978; Lukas, Mendelson, Kouri, Bolduc, & Amass, 1990); while a similar significant reduction in P300 amplitudes in *chronic* alcohol abuse is known to be coupled with increased latencies (Begleiter, Porjesz, & Tenner, 1980; Pfefferbaum, Horvath, Roth, & Kopell, 1979). These findings are similar to the few studies in opioid addiction, with a similar showing of decreased P300 amplitudes and increased latencies (Attou, Figiel, & Timsit-Berthier, 2001; Bauer, 2001; Kouri, et al., 1996; Pfefferbaum, Horvath, Roth, Clifford, & Kopell, 1980). Studies investigating the effects of acute cocaine use have also reported a reduction of P300 amplitude, with little or no effect on P300 latency (Amass, Lukas, Weiss, & Mendelson, 1989; Bauer, 2001;

Herning, Glover, Koeppl, Phillips, & London, 1994; Herning, Glover, Koeppl, Weddington, & Jaffe, 1990; Herning, Jones, Hooker, & Tulunay, 1985).

This low P300 amplitude or P300 amplitude reduction (P3-AR) is thought to be a strong indicator of the state of disinhibition (Bauer & Hesselbrock, 2003; Iacono, Carlson, Malone, & McGue, 2002; Porjesz & Rangaswamy, 2007) and implicated in behaviors associated with early onset of substance-use disorders (Carlson, McLarnon, & Iacono, 2007; Iacono, Malone, & McGue, 2003).

Of particular interest concerning the established understanding of P300 amplitude reduction (P3-AR) in substance abuse is a recent elegant study from Kamarajan and colleagues (Kamarajan et al., 2005) using spatial-anatomical mapping of the NoGo P300 coupled with functional magnetic resonance imaging (fMRI) from a sample of children of alcoholics (naïve to alcohol) . It was found that although the children did not have P3-AR in the Go task – they did have P3-AR in the NoGo condition indicating possible "emotional disinhibition", information helpful to establish a neurocognitive index for the development of other related substance-use and related disinhibition disorders—including opiate addiction.

N100 and N200 and addiction. The N100 is believed to reflect changes in selective attention in that amplitudes increase with increased attention toward task-relevant stimuli (Hillyard & Picton, 1987). Differentially, the N200 reflects a mismatch process associated with the orienting reflex (Ritter et al., 1984) with increases in N200 latency related to increased effort in stimulus discrimination (Pandey et al., 2012). N100 amplitude is decreased with abstinent alcoholics (Patterson, Williams, McLean, Smith, & Schaeffer, 1987; Ritter, et al., 1984) and individuals with a family history of alcoholism (Pfefferbaum, et al., 1979; 1980). In addition, N200 amplitude is reduced and latency is longer in abstinent alcoholics compared to controls in

visual EEG tests (Emmerson, Dustman, Shearer, & Chamberlin, 1987). In addition, decreased visual N100 and increased auditory N200 amplitudes have been found in alcoholics similar to those found in schizophrenia (Olbrich, Maes, Gann, Hagenbuch, & Feige, 2000).

Detoxification and the P300. Changes in P300 amplitude and latency following detoxification have been seen in drugs of abuse including decreased P300 amplitude after alcohol (Begleiter, et al., 1980; Kouri, et al., 1996) and increased P300 latency in abstinent cocaine users during the first twenty-four hours following withdrawal; this returns to control levels as early as day two. In addition, increased P300 latencies are seen during the first two weeks of withdrawal in chronic cocaine users but no abnormalities in P300 amplitudes (Herning, et al., 1994; Herning, et al., 1990); P300 latencies return to control levels by the fourth week of treatment with no significant reaction time or error differences in a visual or memory task between subjects and controls.

Few studies on opiate detoxification and CNS function have been published. Perhaps ERP measures can pick up subtle changes in cognitive function that exist in absence of behavioral impairment, or index the fact that brain dysfunction can come before any observable behavioral impairment following detoxification. Years ago, Guerra, Sole, Cami, and Tobena (1987) assessed attention improvement in opiate-dependent individuals after one month of abstinence using memory and verbal fluency tasks. Initially the addicts were significantly more impaired than matched controls, but not after detoxification; this gives hope for some recovery of brain function following the detoxification needed for substance abuse and addiction.

Although ERPs have been a valuable tool to monitor electrical events that parallel the development of drug tolerance and withdrawal, there are still no published reports on neurophysiological measures of visual attention and color processing in withdrawal in opiate

addicts. Investigation into the electrophysiological changes associated with visual processing of color in opiate tolerance and dependence is critical for our understanding of how neuronal mechanisms for relapse may be either ameliorated or exaggerated in opiate addiction.

Physiological Markers of Addiction: EEG and Electroretinogram (ERG)

The physiological markers of addiction, namely EEG and ERG, are particularly relevant to this proposal, as positron emission tomography (PET) studies are not a practical option. Thus, a review of the evidence for physiological markers of addiction will be given. EEG studies provide consistent evidence for frontal lobe changes in the form of excess relative alpha power (i.e., brain waves oscillating at 8 to13cycles per second—relaxed, somewhat disconnected, self-reflective , not attentive), deficit of absolute and relative delta (i.e., brain waves at less than 4 cycles per second; in deep sleep), and theta power (i.e., 4 to 7 cycles per second; time just before drop from Beta awareness to Delta sleep state) and increased beta activity (i.e., brain waves at 14 to 30 oscillations per second, totally awake and active) in chronic substance abusers (Herning, et al., 1994; Luck, 2005; Noldy, Santos, Politzer, Blair, & Carlen, 1994; Prichep, Alper, Kowalik, & Rosenthal, 1996; 1996; 1995). The reported EEG changes, especially the delta deficit in the frontal cortex, are thought to be related to the mesocortical dopamine system and sensitization where it may be responsible for the abnormal gating to external stimuli. Studies of ERPs have reported reduced frontal P300 with possible correlation to relapse and three distinctive subtypes of patients based on specific mathematical analysis of their baseline quantitative EEG changes (Prichep et al., 2002). These changes correlated highly with retention in treatment, but not with duration or severity of drug use.

The electroretinogram (ERG) is the recording of electrical potentials from the retina in response to flashes of light (Elkashef & Vocci, 2003). The human retina contains 4–6 million

cones. Cones are responsible primarily for pattern detection and color vision. Color vision is mediated by three different types of cones, long, medium and short, based on their spectrum absorption (Conway, 2009; Mullen, Dumoulin, McMahon, de Zubicaray, & Hess, 2007; Shapley & Hawken, 2002). Short cones respond to blue light. There are few ERG studies that look at ERG gender differences but a recent dark-adapted electroretinogram study using blue and red flashes found that the implicit time for the b-wave was delayed significantly for the male group (Lim & Ohn, 2005).

Dopamine and the retina. There are two types of Dopamine (DA) cells (amacrine and interplexiform) in the human retina (Fried & Masland, 2007)—both receive presynaptic input from cone bipolar cells. DA cells modulate the input from cones to other common neurons and directly modify the photoreceptor signal. Light stimulates L-aromatic amino acid decarboxylase activity leading to increased synthesis of DA from l-DOPA and subsequent release of DA which binds to D2 and D4 receptor types that have been identified on cones.

Patients with decreased DA tone (e.g. Parkinson's disease patients or schizophrenic patients on neuroleptics) have abnormal ERGs (Archibald, Clarke, Mosimann, & Burn, 2009; Buttner et al., 1993; 1994; Hirayama & Ishioka, 2007; Hofer, Carroll, Neitz, Neitz, & Williams, 2005; Muller et al., 1998; Olsson, et al., 2009; Roy, Roy, Smelson, Brown, & Weinberger, 1997; 1997), particularly reduced blue cone amplitude (Sartucci et al., 2003). Regarding substance abuse, 60% of cocaine-withdrawn patients, for example, have reduced blue cone b-wave amplitude as seen in other ERGs; this reduction is known to correlate with cocaine craving (Desai, Roy, Roy, Brown, & Smelson, 1997; Roy, Roy, Berman, & Gonzalez, 2003; 1997; 1997; 1996; Smelson, Roy, & Roy, 1996; 2001).

Cognitive/Neuropsychological Markers of Addiction

Most studies suggest that chronic substance abusers have some deterioration in cognitive function, specifically attention, reaction time, verbal memory and visuospatial construction (Bauer, 2001; Strickland et al., 1993). Thus, neuropsychological testing may show some promise as tools for studying addiction, in particular reaction time, selective attention, and visual processing especially those neural substrates that engage the natural reward system in spontaneous selection and perceptual preferences such as the hippocampal cortex—a high density area of cortical mu-opioid receptors long thought be involved in spontaneous selection of visual information (Bigler & Fleming, 1976; Yue, et al., 2007).

Visual Processing and Attention

Research in visual attention involves discovering how individuals process and interpret information within their visual field (Geng & Behrmann, 2003). This includes identifying how cognitive and neural components interact to select certain information and inhibit other information for further internal analysis. Within this broad area many theories have been developed regarding how meaningful visual information is discriminated from distracting stimuli. The Feature Integration Theory (FIT) was originally developed by Anne Treisman (1994) to account for how visual processing of information occurs. This theory proposes that information must initially meet certain target criteria before it is selected for further evaluation (Geng & Behrmann, 2003).

Treisman (1994) expanded her original explanation of FIT to account for separate attention parallel coding procedures. For example, when participants are given advanced location information, they use an "attention window" to narrow their visual field by selectively searching a specific location. When then given advanced information regarding relevant stimuli,

participants use inhibition to disregard irrelevant stimuli and make their selection. Further, when participants are not given any advanced information, they choose an area within their visual field to serially scan until the target stimulus is found (Treisman, 1994).

An interesting phenomenon that occurs in visual attention mechanisms is the "pop-out effect". This automatic response takes place when an object within the visual field has characteristics which make it unique from surrounding objects. This contrast results in the unique object "popping-out" from the background and immediate attention is focused on it (Krummenacher & Müller, 2005; Li, Gratton, Yao, & Knight, 2010). Wolfe (2003) has argued that pre-attentive processes (such as those which result in the pop-out effect) rely on categorical information and enable quick identification of potential objects in a visual scene for more comprehensive analyses. In other words, pre-attention does not occur independently of normal selective attention processes, but works to enhance the overall search mechanism (Li, et al., 2010; Lieb et al., 1999).

Sex Differences in Visual Processing

Male versus female differences in the retina. In a review for educators with regards to student engagement and needing to be aware of sex differences in learning, Susan J. Kovalik (Kovalik, 2008) , discusses how a females's retina may be built differently from a male's and therefore when a female and a male look at the same landscape, they may see different images (Baccus, Olveczky, Manu, & Meister, 2008; Ogueta, Schwartz, Yamashita, & Farber, 1999; Olveczky, Baccus, & Meister, 2003, 2007). In a study done immediately after 102 babies were born they were given a choice between looking at a simple dangling mobile or at the face of a woman who smiled but didn't say anything; all were videotaped. Researchers blind to the sex of the babies, tracked their eye motions. The differences were significant with the boys being twice

as likely to look at the moving mobile while the girls looked at the living face (Oliver-Rodriguez, Guan, & Johnston, 1999).

Very little is known about the structural differences of the rods and cones within the retina in regards to male and female eyes (Cowey & Stoerig, 2001; Sumner, Anderson, Sylvester, Haynes, & Rees, 2008), however in study on the organization of the human trichromatic cone mosaic it was found that males and females had nearly identical short(S)-cone densities while males varied in the ratio of long (L) to middle(M) wavelength cones, this may help explain gender differences in visual color processing (Greene & Gynther, 1995; Hofer, et al., 2005). Rods are sensitive to a single photon and create only one coarse gray image while cones are less sensitive to light, thus they need more light; the ability to see fine detail is cone dependent and there are approximately 18 times more rods than cones in the human eye (Kolb, 2009).

Both rods and cones send their signals to the ganglion cells, some of which are large while others are small; however, they have different jobs. The large cells are wired to rods and are sensitive to motion (Baccus, et al., 2008; Fried & Masland, 2007; Olveczky, et al., 2003, 2007). Psychologically one would think of them answering the questions, "Where is it now?" and, "Where is it going?" The male retina has mostly these larger, thicker M (magnocellular) ganglion cells, and can track objects anywhere in the field of vision (Vaegan & Hollows, 2006). The smaller cells (cones) answer the questions, "What is it, and what are the colors and textures?" The female retina has predominantly the smaller, thinner P (parvocellular) ganglion cells which are concentrated in and around the fovea, the center of the field of vision (Vanni, Henriksson, Viikari, & James, 2006). The male eye structure is geared to motion, therefore looking out the window or out the classroom door, watching the classroom action, and anything moving will catch boys' attention (see Cowan et al., 2000; Wager, Phan, Liberzon, & Taylor,

2003). Kovalik (2008) thought this may be a key element in understanding why males have the high rate of being diagnosed with attention deficit disorders; certain P300 studies that looking at endophenotypes of boys at risk for disinhibitory disorders seem to substantiate this notion (Iacono, Carlson, & Malone, 2000; Iacono, et al., 2002; Okun & Lampl, 2008; Roussos, Giakoumaki, & Bitsios, 2009).

A recent study by Steffensen and colleagues (2008) examined event-related potential (ERP) gender differences of the pop-out effect using a visual object "Go/NoGo" recognition task. Participants were asked to distinguish between *Relevant*, *Standard*, and *Irrelevant* stimuli presented in a matrix fashion that indicated P300 and N400 amplitudes were greater in females than males to Relevant stimuli, however, the P700 amplitudes associated with the *Irrelevant* stimuli did not show any significant gender differences. The sex differences obtained in this previous study raised the question as to whether the same differences could be observed when visually processing color paradigms in not only controls but more significantly in opiate abusers while in the addictive state similar to that seen in cocaine abusers (Desai, et al., 1997), and those with Parkinson's disease (Sartucci, et al., 2003).

Genetic Markers of Addiction

There has been a swing over the past decade in understanding of the etiology of addiction, asking how much is environmental and how much is genetics—encouraging the investigation of how genetics and environmental factors interact (Bennett et al., 2002; Caspi et al., 2002; 2003). With such discovery, drugs and therapies can potentially be better refined and individualized to clients. If such theories prove to be true, risk and outcome can be better predicted, ultimately providing society with valuable resources to treat additional clients. One of the major areas of focus since this discovery of genes only producing risk and addictive disorders

in specific environments is the new field of *pharmacogenetics* which focuses medical treatments according to genotype background. Naltrexone, for example, works much more effectively, if at all, only in clients with opiate genotypes that *modify* the mu opiate receptor, a major site for drugs of abuse (Anton, et al., 2008; Ray & Hutchison, 2007), suggesting that the potential for drug treatment efficacy may be based on genetic background (Linnoila et al., 1994).

Summary and Hypotheses

Phase I of the current study was an investigation of how control or drug-free participants visually process color information (Brigham Young University [BYU] students are nationally recognized as being relatively drug-free) and any sex differences found in visual color processing in drug-free participants through a continuation of prelimary studies using electroencephalography (EEG) measuring latencies and amplitudes of visual evoked potentials (VEPs), in particular the P300 and the P700, of males versus females. It was found that select event-related EEG potentials (ERPs), including the P300 and P700, are greater in females than males in visual processing of objects, suggesting that women attend to and process visual information, especially distracting information, differently than men (see Steffensen, Ohran, et al., 2008). The current study extended the previous study to evaluate if ERPs vary between males and females using a color discrimination Go/NoGo processing task.

Phase II was to investigate how substance abusers and addicted participants visually process color information using electroencephalography (EEG) measuring the latencies and amplitudes, in particular the P300 and the P700, of males versus females substance abusers and opiate addicts. The following hypotheses were associated with these investigations:

H_1) *It is hypothesized there will be sex differences in ERPs in visual processing of color including a color discrimination task; particularly in the processing of the color blue.*

H_2) *It is hypothesized there will be sex differences in ERPs in opiate addicts for simple Go/NoGo task in visual color processing tasks, particularly in the processing of the color blue.*

H_3) *It is hypothesized that there will be differences in ERPs between drug-free controls and opiate addicts for visual color processing tasks, in particular ERP differences in the processing of the color blue.*

CHAPTER 3

Methodology

Participants

There were ninety-eight initial participants in this study made up of four groups: Male controls (n = 30; age range = 17 – 53 years); female controls (n = 30, age range = 18 – 56 years); male addicts (n = 19, age range = 18 – 53 years), and female addicts (n = 19, age range = 18 – 51 years). The control groups were matched as closely for age as possible with the addicted groups. After individually looking at the neurophysiological data collected for all subjects related to the current study the data from seventy-five were retained for inclusion in the final analyses: Approximately twenty-seven percent of the EEG data collected were found to have recording discrepancies from undetected sensor net damage which may have been due to damaged electrodes on head nets associated with prior heavy use (e.g., possible electrode plate corrosion, non-conducting sponges), noted run time errors or amplification disconnects, and too many human errors or eye-blink artifact), and one male control was excluded for incompletion of the testing. This gave a final sample size for analyses of 75 participants: Male controls = 24; female controls = 22; male addicts = 16; and female addicts = 13.

Inclusion Criteria

Controls. Thirty female and thirty male control participants were recruited from Brigham Young University undergraduate psychology and neuroscience classes and from the local community via announcements (in classes) and "word of mouth," and IRB approved flyers (posted on BYU campus and housing bulletin boards). Participants ranged in age from 17 – 56 years and were screened to ensure they were in good overall health, with no personal history of

physiological or psychological disorders, and/or head trauma, and weren't taking any medication. Participants for the non-clinical control group inclusion criteria were: Drug-free male or female, age 18-55 years, no prior history of severe brain injury, seizure free, not prone to fainting, not claustrophobic, be willing to indicate all drug use on drug history sheet, and not have used opioid pain killers in the last three months, sleep aids in the past month or other mood altering prescription drugs, willing to give a urine sample for urinalysis (UA), willing to spend 2 hours participating in neuropsychological and EEG testing, willing to keep confidential all proceedings and take offered compensation (e.g., extra credit for a psychology or neuroscience class) and a packaged food item. After a complete description of the study to the participants, written informed consent was obtained from all participants.

Addicts. Nineteen female and nineteen male opiate-dependent participants were recruited from a community-based high intensity residential substance abuse and detoxification treatment program. This is a state funded residential short-term (30 days or less) and long-term (more than 30 days) detoxification and addiction treatment center for treatment of persons with or without co-occurring mental and substance abuse disorders which provides a vertically integrated continuum of care according to the most currently published American Society of Addiction Medicine (ASAM) Patient Placement Criteria. (for further information see http://www.utahcountyonline.org/dept/HealthSubst/Treatment/index.asp).

The therapists, counselors and intake staff were contacted by the PI(jp) and asked to help recruit those with an opiate addiction diagnosis. They were provided with an electronic copy of the Brigham Young University (BYU) Institutional Review Board (IRB) approved substance abuse participant recruitment flyer for inclusion or exclusion. The Pre-screen Checklist was then reviewed by the therapist with those clients interested in participating in the research project (See

Appendix B for Pre-Screening Checklist). Inclusion criteria were: Males or females diagnosed with opiate addiction, age 18-55 years, still experiencing daily craving for drug, no prior history of severe brain injury, seizure free, not prone to fainting, not claustrophobic, be willing to indicate all drug use on drug history sheet, and not have used opiates in past 24 hours or longer than 60 days out, willing to give a sample for urinalysis (UA), willing to spend three hours being escorted to and from the BYU EEG facility with two hours of neuropsychological and EEG testing; keep confidential all proceedings and take offered compensation—$ 20.00 Visa gift card and a packaged food item.

All participants were matched as closely as possible for age and gender ranging in age from 18 – 56 years and were pre-screened to ensure they were in basic good overall health, had good eyesight and matched. However, it is understood that the addicted cohort was in withdrawal from opiate dependence and addiction, having had prior assessment through a state run treatment program as to their need for opiate addiction treatment by either a Licensed Substance Abuse Counselors (LSAC) or Licensed Clinical Social Workers (LCSW) trained to do intake assessment. After a complete description of the study to the participants, written informed consent was obtained from all participants.

Confidentiality. Participants were given research identification numbers and all data was stripped of unique identifiers (e.g., name, date of birth). Data is stored in a secure (password-protected) database and consent forms are secured in a locked filing cabinet at the BYU UPC Center and/or on the 12th floor of the Spencer W. Kimball Tower (both facilities have limited access and require keyed entry to access). The study was performed with strict adherence to Brigham Young University IRB regulations.

Behavioral Tests Used

In the current study all participants were given the same battery of prescreen checks, questionnaires, neuropsychological tests, and computer testing, tested for handedness and eye dominance. The cognitive behavioral testing was done both by standardized "pen and paper" neuropsychological tests. Reaction time and physiological responses were measured with EEG, and recorded during a battery of computer screen Go/NoGo tasks. The battery of three cognitive, physiological and behavioral tasks (i.e., the *Finger Tapping Test*, the *Symbol Digits Modality Test*©, and the *Trails A or B* tests, were used to provide the necessary scientific rigor to evaluate the utility of object versus color processing as an objective index of the addictive state from electrophysiological testing which included a short visual color discrimination test meant to also measure sustained and directed attention (e.g., shortened adaptation for the computer of the *Stroop Effect Test*, Stroop, 1935), an object recognition task, and a set of three visual color processing tasks randomly assigned. Male and female participants were asked to participate in a single session of neuropsychological testing and separate physiological recording session; all were presented with the same tasks. (See Appendix E for Table E1 with t-test comparisons of neuropsychological testing results by addiction and gender).

Procedures

Scheduling of participants. The majority (85%) of the participating substance abusers were assigned a time either morning or early afternoon (to avoid fatigue or any treatment program conflicts) over a two week time period. Each participant was picked up individually by the PI and one Research Assistant (RA) via a car rented for insurance purposes, brought to the BYU testing facility and then returned following the testing session. The control participants'

testing were at random times of day and into the evening to allow for different class schedules and other considerations—they signed up to be in the study via SONA® a program used to facilitate research study participation in the BYU psychology department.

Assessment Session Protocols

Consent forms. Upon arrival at the EEG testing rooms all participants were seated in a comfortable chair and given the opportunity to thoroughly review the consent form with the PI (see Appendix B for consent forms). Once signed consent was given they were asked to complete a computerized demographics/screening questionnaire.

Demographics/screening questionnaires. Each potential participant was asked to fill out an on-site computerized questionnaire (see Appendix B for hard copy) prior to the EEG session to determine whether they met study qualifications. Once pre-qualification criteria were met, participants were scheduled for an EEG session and given a complete description of the study and written consent was obtained.

Urinalysis (UA) drug screening test. In order to verify that every participant was truly drug free all participants that were specifically age and gender matched to the substance abuser group were given the same urinalysis (UA) test that is normally given randomly in the treatment program to check for compliance to their programs (Charles, et al., 2003)—all others completed the drug disclosure questionnaire See Appendix B4. This UA tests for a variety of illicit drugs including opiates, marijuana/THC, cocaine and amphetamines and benzodiazepines and PCP. All participants were tested and UA samples were collected prior to testing (there were nearby bathroom facilities to allow for privacy and secure freezers are the site; storage time of any frozen UA sample was minimal). The same type of testing kit was used for all. The UAs were de-identified, frozen immediately, and taken within 48 hours to the tested at the treatment

program for a stringent Research Institute on Addictions (RIA; University of Buffalo, New York)analysis. It should be noted that as a publically funded facility, the participating treatment center is under 42 CFR Part 2 Law and required to meet very stringent confidentiality and HIPAA regulations. Only the PI(jp) handled any of the UA samples after the participant placed them in a box for frozen storage at BYU before being taken to the treatment center for testing.

Each UA sample was labeled with a coded identifying number only, and that number plus date of sample and research ID number was used to identify it. The participants were advised of their confidentiality rights and took all of the other tests at the same time the UA sample was given. A positive UA resulted in disqualifying the subject data due to drugs in the system—no assessment was discarded because of a positive UA. If the participant was unable to give the required sample at the beginning we would ask regarding it at various times of the testing so a good undiluted sample could be given.

All participants (controls and addicts) completed a drug screening questionnaire listing all drugs used, amounts, when last used and when drug abuse started as applicable (See Appendix B for drug use/screening questionnaire).

Handedness and eye dominance. Each participant was then checked for handedness, eye dominance and age, and then tested for any visual color deficiency.

Neuropsychological Tests Given

Hardy-Rand-Rittler (HRR) Pseudoisochromatic test. Each participant were administered the HRR visual color test—this was a 5 minute color deficiency test given prior to having the EEG net placed at the recording session to determine the extent, if any, of any color deficiency that may have been unknown—no one with a color deficiency was included in the testing. The test is a series of color plates shown to the participant who responds to certain

questions of "How many?," "What?," and "Where?" of any symbols seen on each plate (given in varying degrees of color embedded in a grayscale background) by verbal response and by tracing with a brush any symbols seen.

After completion of the color deficiency test each participant had the following three neuropsychological tests administered (by PI) as listed below:

Finger Tapping Test: (5 minutes). This is a straight forward neuropsychological test used to assess motor speed and motor control (especially in those who have experienced some type of brain injury) and is a simple finger tapping test that can measure and compare the participants' reaction time. Participants placed their dominant hand palm down, fingers extended, with the index finger resting on a lever that was attached to a counting device. Individuals were instructed to tap their index finger as quickly as possible for 10 seconds per trial, keeping the hand and arm stationary and were not allowed to hold the hand down. This trial was repeated five times on each hand, with hand changing every two times per hand until 5 trials per hand were completed—this change was done to avoid great hand fatigue. Before starting the test, individuals were given a practice session.

Symbols Digit Modalities Test© (SDMT): (5 minutes). The SDMT© involves a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee was given 90 seconds to pair specific numbers with given geometric figures. Responses were written but could be oral if necessary, for either response mode, administration time takes just 5minutes with simplified scoring. Individuals with cerebral dysfunction perform poorly on the SDMT©, in spite of normal or above average intelligence. This test was used because it has been proven for its effectiveness in a wide range of clinical applications, including: Head injuries; strokes; brain tumors; reading difficulties; learning disorders;

Alzheimer's disease; viral, bacterial, and other cerebral infections; pre-, peri-, and early postnatal insults; senile dementia; aphasia; neurotoxicity; alcoholism; cerebral anoxia; Huntington's Disease.

Trail Making Test, Parts A or B. (5 minutes). The Trail making Test is a neuropsychological test of visual attention and task switching which was given randomly with one-half of the participants being given Part A and the other half given Part B to allow for a second testing if necessary and no test-retest confounds. This test consisted of two parts and provided information about visual search speed, scanning, speed of processing, mental flexibility, as well as executive functioning. Part A is a page with 25 numbered circles randomly arranged. Individuals are instructed to draw lines between the circles in increasing sequential order until they reach the circle labeled "End." Part B is a page with circles containing the letters A through L and 13 numbered circles intermixed and randomly arranged. Individuals were instructed to connect the circles by drawing lines alternating between numbers and letters in sequential order, until they reached the circle labeled "End." If the participant made mistakes, the mistakes were quickly brought to their attention, time was stopped, and then they continued from the last correct circle. This test takes approximately five to 10 minutes to complete. This test was originally known as Partingon's Pathways, or the Divided Attention Test, which was part of the Army Individual Test Battery and evaluates information processing speed, visual scanning ability, integration of visual and motor functions, letter and number recognition and sequencing, and the ability to maintain two different trains of thought. The test can be administered orally if an individual is incapable of writing. Poor performance is associated with many types of brain impairment, in particular frontal lobe lesions.

Evoked-Potential Recording

Key press instruction. After neuropsychological testing was completed the participant was sat in front of a computer to be given a practice trial of the Binocular rivalry test at the end of the computer task session. They were instructed on how to wear the 3-D glasses and key press using two fingers rather than the usual 1 finger press for response.

Sensor net. At this point the participant's head was measured to determine the size needed—being snug is important. This was done by measuring first the circumference of the head from ear to ear around the head —this is used to determine the right size of sensor net needed. Then the head was measured from ear tragus to ear tragus (small protruding bumps in front of ears) over the top of the head with a grease pen used to mark the half-way spot on the top of the head. The head was then measured from nasion (bump between eyes and at top of nose) to the inion, or external occipital protuberance (bump on lower rear part of skull) and the scalp was again marked where it crossed the other ear to ear mark on top of the head. This established the center of the head where the Cz REF electrode on the sensor net (center of net) was to be placed to get good spherical tension and proper signal reading. The sensor net was soaking in the special potassium chloride and baby shampoo solution for improved electrical conduction while this was being done—2-3 minutes.

The participant was given a towel and a washcloth to help keep from getting wet from the saline solution and asked to close their eyes while the net was placed (two people placed the net allowing for better fit—see Appendix C for example of a well-placed sensor net).

Sensor net specifications. This is a 128-channel sensor net designed to acquire dense array EEG data; it has sponge inserts in each electrode pedestal allowing the electrolyte saline

solution to be held for 2-hour recordings. The Geodesic EEG System (GES) HydroCel Geodesic Sensor Net (HCGSN; Electrical Geodesics, Inc., Eugene, Oregon) is specifically designed to give surface tension and even distribution of the electrodes across the spherical surface of the head. The networking on a HCGSN adjusts the spatial location of each sensor until a single distance spans all pairs along direct lines, each line being a *geodesic* (i.e., the shortest distance between two points on the surface of a sphere) for the active and grounded sites. An accurate geodesic tessellation of the head surface optimizes the sampling of the electrical field. This accurate surface sampling allows for integration of advanced EEG methods, specifically anatomical magnetic resonance images (MRI) or functional MRI (fMRI).

The internationally accepted 10-20 placement system of the sensor net's electrodes (electrodes are placed at 10% and 20% along lines of latitude and longitude) was used for montage points of the Average-Reference Mastoid Montage (as seen in Appendix C1) as established in the 1950s by the *International Federation of Clinical Neurophysiology* (Jasper, 1958). See Appendix C2 for a top and side view of how the electrodes are to be placed for use in analyses of the visual evoked responses (VEPs) electrophysiological data measured by the EGI 128-channel HCGSN in the current study. VEP's were acquired in 1-second epochs 100ms before stimulus and 900ms after the stimulus for each visual stimulus presentation. E-prime Software (Psychology Software Tools, Inc., Sharpsburg, PA) was used for the visual attention tasks, which were transmitted to a computer screen (68 cm) in front of the participant and to a screen in the recording room.

Impedance checks. Once the net was placed the participant was taken into the shielded EEG room with the amplifier and sat in a comfortable chair about 62 cm from the computer monitor making sure no metal was being touched by the participant that could ground the head

electrical activity. The net was then plugged into the amplifier and the EGI and E-prime software connections were established and any impedance to current flow was checked until it was reduced to 10 Ohms (10kΩ). Impedance measures were checked between each session to account for any evaporation of electrolyte solution during the computer testing. Participants were asked to come with freshly washed hair with no conditioners or gels in order to ensure good conductivity. The participant was then shown how wiggling in the seat, nose scratching, clenching their teeth, blinking their eyes a lot, etc. could change the output of the data on the EEG and how sensitive the sensor net was to component generation.

Once it was established that the systems were running correctly the lights were dimmed and the first set of instructions were given on how to respond to the stimuli. Participants were told to press a button as directed in the instructions given at the beginning of each computerized task. When the task began, each participant read a standard set of instructions explaining the task and sample visual stimulus were shown on the computer screen. Reaction times (RT) were measured from the time the stimulus was presented until the participant pressed the button. If the participant correctly detected the target, the words "correct" and the RT were displayed on the computer screen 500 ms after the response. When target was present and participants did not press a button, the words "no response detected" were shown on the screen. An incorrect response notice appeared on the screen if participant pressed the button when no target was in the matrix.

Computerized Programs

Stroop-effect test: (5 minutes). We administered a 5 minute computerized, 4-phase Stroop-like effect color test for cognitive testing (i.e., word recognition, color recognition, color naming of an incongruent word, word naming of an incongruent color), and to assure the

participants were capable of doing all of the tasks (Stroop, 1935). capturing via computer all stimulus times as well as participant responses. (It should be noted that this task was not included in the current study statistical analyses; all timing and EEG data collected will be analyzed in the future for sex differences.)

Color processing task: (12 minutes). This was a "Go/NoGo cognitive test." In a task consisting of three separate sessions or blocks (four minutes duration each) of flashing Red, Green, and Blue lights on a computer monitor, participants were asked to respond via key press when they detected the presented Relevant stimuli (either Blue, Red, or Green as instructed in the programing of each session—no one knew what color was to be Relevant at any given time including RAs or PI). The stimuli were randomly presented (50 ms duration) on a computer monitor and participants were instructed to not to respond when Irrelevant color flashes were shown. For example, if instructions were given to respond to Blue when presented then the participant was to key press as quickly as possible (Go) but to ignore and not respond (NoGo) to the Red and/or Green flashes. Instructions were exactly the same for each color when Relevant. This was designed to compare the ERPs for each color wavelength responded to when either Relevant or Irrelevant. Each session began with a block of three practice presentations followed by 40 test presentations of each of the three stimuli, randomized by condition, and interval.

Object recognition Task: (8 minutes.) Three 3X3 matrices were randomly presented at 2-4 sec intervals during the 12 min recording session (i.e., Relevant, Irrelevant, and Standard stimuli). One object in the Relevant matrix of right-pointing arrows is a diamond symbol and one object of the Irrelevant matrix is a variation of a diamond and an arrow. Regardless of matrix, these elements are readily distinguished and "pop-out" from the other eight elements of each matrix, despite being presented to the participant very briefly (50 msec). The participant was

instructed to only respond with a key press to the "open" diamond. (see Appendix D for a report on this concurrent EEG study of an object recognition task).

Binocular rivalry*:* **(3 minutes).** Participants put on a pair of 3-D glasses with red gel lens on one side and blue gel lens on the other. They were advised to gaze at a static picture on the computer screen of a rivalrous stimulus consisting of an electronic picture of the number 1 and the number 2 separately defined by red and blue luminance variations – the number 1 in red and the number 2 in blue (Shapley & Hawken, 2002). Due to *binocular rivalry* the images initially appear to be superimposed on each other but when seen through a red filter over one eye and a blue filter over the other, only the "1" was visible through one eye and only the number "2" through the other eye. The participant was advised to fixate on the computer screen and each scan of the numbers should present separately to the participant—the number 1 (in red) would appear separately to the eye with the red gel lens and the number 2 would appear separately to the eye with the blue gel but the brain would perceive it as if both eyes are seeing just one or the other.

Binocular rivalry allows for depth perception but normally we see things as "on-top" of each other unless the stimuli are screened out by use of the 3-D glasses. As they fixated on the computer stimulus the participants were to press the key that coordinated with the number they saw individually as binocular rivalry took over the perception process. (It should be noted that this task was not included in the statistical analyses of the current study analyses and that the timing data collected from this rivalry processing is to be measured in the future as perception alternated back and forth with each number and will be matched to the EEG data for any sex differences in oscillation time and number of key presses.)

Following the final computerized test and the assessment session the participant's net was unplugged from the amplifier and the net was carefully removed from their head. They were invited to go "freshen up" if they felt so inclined in the nearby washroom and advised that the red indentations from the electrodes would disappear in a few minutes. Each participant was then taken back to the starting room and thanked for their participation given their packaged food item and gift card or the PI entered the required information on SONA® to verify student involvement in the project. The net was disinfected using proper procedure as outline by EGI and the participant was then either escorted to the elevator for departure or returned to the residential treatment center via a rented car used for this explicit purpose.

Electrophysiological Testing Equipment and Software

Data processing software. E-Prime Software (Psychology Software Tools, Inc., Sharpsburg, PA) was used to run the visual attention task and the stimuli were presented on a PC-type computer screen. The Geodesic EEG System 300 was used to record EEG activity and participants wore a 128-channel sensor net during each session—sized to fit their individual head size. The Geodesic system is programmed to monitor any EEG artifacts automatically and flagged potential artifacts associated with excessive head, muscle or eye-blink movements. Evoked potentials were acquired in 2 second epochs during each visual stimulus presentation; they began 100 milliseconds prior to and ended 900 milliseconds after each stimulus presentation. The EEG data around each visual stimulus were averaged to obtain the visual evoked potentials (VEPs) from all participants.

Statistical Analyses

The EEG around each visual stimulus was averaged to obtain the VEP for each participant. At each electrode, the visual presentations were averaged. Amplitude and latency

were measured for each peak of the within-subject average VEP components for the N100, P100, N200, P200, P300, late negative or N400, and late positive (LP) or P700 waveforms, using NetStation® Data Analysis Tools (Electrical Geodesics, Inc., [EGI], Eugene, OR).

The quantitative electrophysiological data obtained through the EGI Data Analysis Tools were analyzed using the SAS/STAT® Proc Mixed statistical analysis program (SAS Institute Inc., 2008). This statistical program was meant to fit multilevel and hierarchical linear models and considered suitable for the "mixed" statistical data from the current study; data on individuals were nested within naturally occurring hierarchies such as male and female within addiction. It was also considered that a multivariate analysis was not necessary since there was a great deal of significance found in almost all hypotheses analyses. Igor® software (WaveMetrics, Lake Oswego, OR) and Excel (Microsoft Office) were used to present the data in graph and picture form for easier reading. Measures of Reaction Times (RT) were analyzed with ANOVA.

Ethical Considerations

Confidentiality and HIPPA compliance. Prior approvals and permissions were received from both the Director of the addiction treatment program where all substance abuse participants were recruited and from the Brigham Young University Institutional Review Board. All data were handled with confidentiality and with compliance to HIPAA regulations. Signed consent forms were received before any testing started and any amendments or changes to the defended prospectus protocols etc. were met with approval from Brigham Young University's Institutional Review Board (IRB). Strict adherence to ethical issues and research standards were maintained.

CHAPTER 4

Results

Analyses of Electrophysiological Data

In the current study twenty nine participants diagnosed with opiate addiction (16 male, 13 female) and 46 age- and gender-matched non-clinical controls (24 male, 22 female) were statistically analyzed for hypotheses comparisons by using EEG data collected.

Hypothesis One (H_1)

H_1) *It is hypothesized there will be sex differences in ERPs in visual processing of color including a color discrimination task; particularly in the processing of the color blue*.

Results Summary

Gender Differences in Visual-Evoked Potentials (VEP) and Event-Related Potentials (ERPs) in the Color Recognition Task

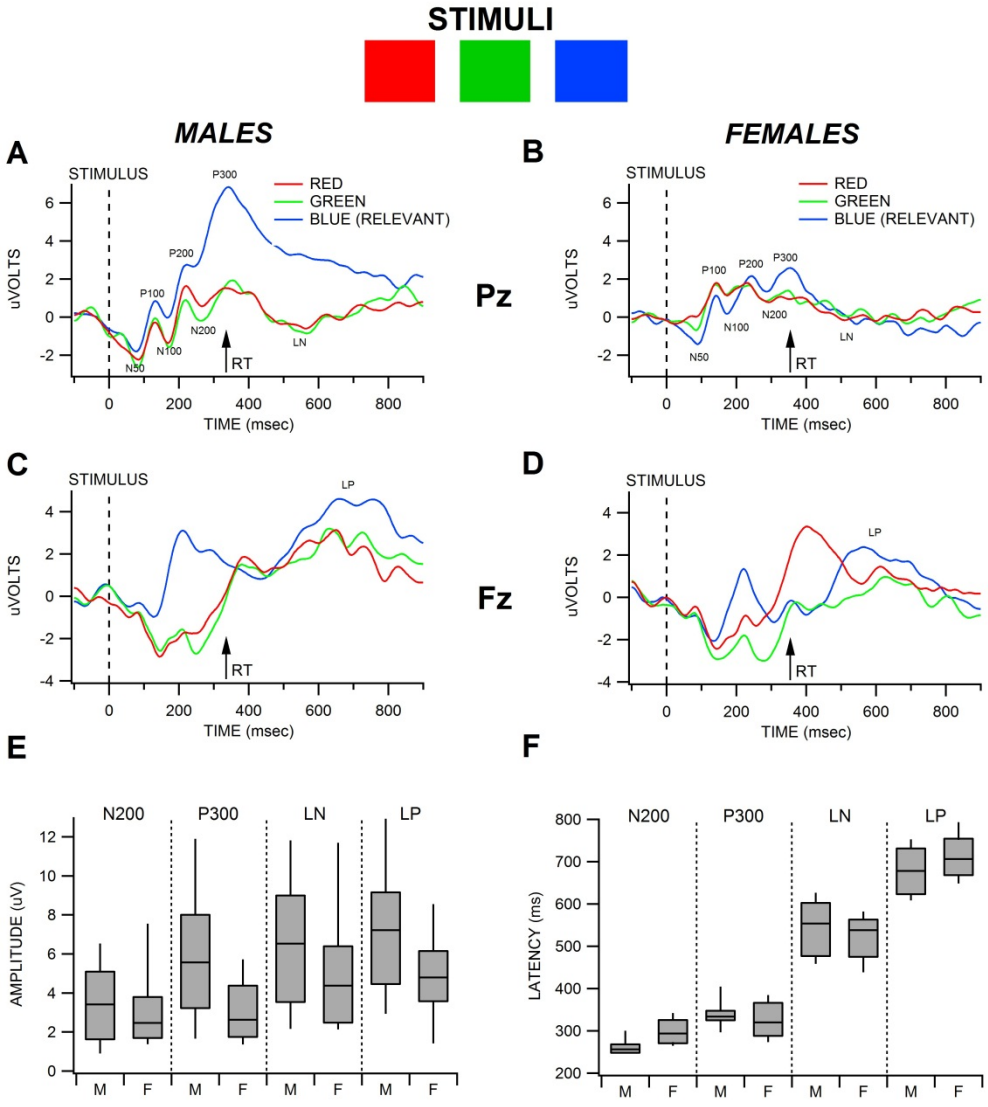
In the color recognition task, stimuli (50 msec duration) were randomly presented at 2-4 sec intervals during the 12 min recording session (i.e., Red, Green, and Blue stimuli). Subjects were instructed to press a key pad button when the Relevant stimulus was presented. A comparison of VEPs elicited by Red, Green and Blue stimuli superimposed at electrode Pz in male and female controls in the color recognition task are shown in Figures 1A,B and at electrode Fz in Figure 1C, D.

It was found that the parietal and occipital electrode sites evinced the most well-defined combination of early (i.e., task-independent) and late (task-dependent) components of the VEP. The averaged VEP consisted of multiple components which were identified by their respective

positions on the waveform, relative to the time of stimulus presentation. Eight distinct alternating positive/negative peaks on the VEP waveform were identified, which occurred at characteristic latencies from the time of stimulus presentation. Early and late peaks of the VEP were identified according to established convention and were labeled N50, P100, N100, P200, N200, and P300, respectively. Two late VEP components, termed the late negative (LN) and late positive (LP), were also identified.

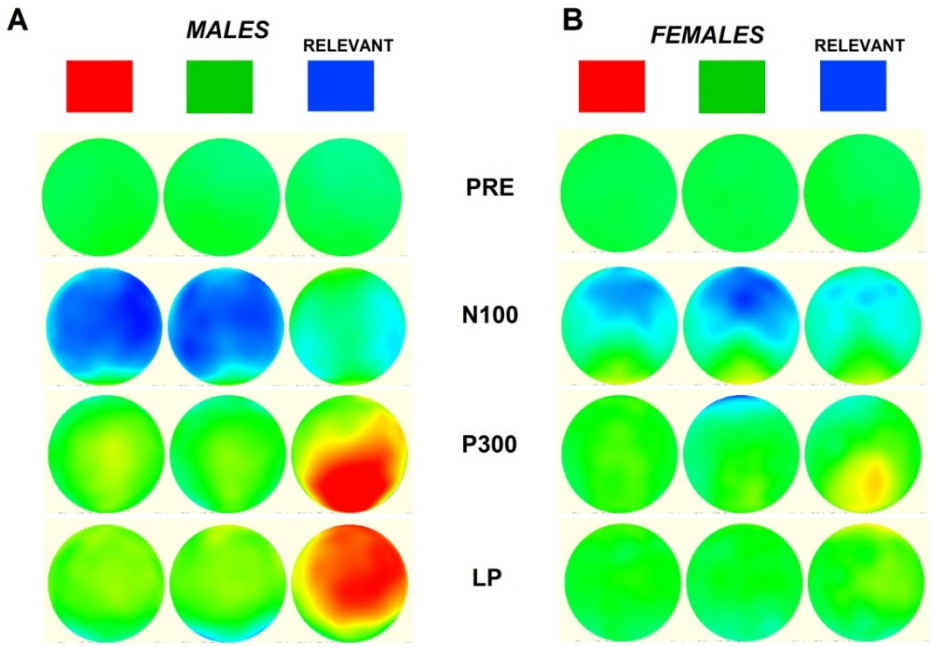
While the early components (i.e., N50, P100, N100, and P200) of the averaged VEP waveforms were relatively unaffected by type of visual stimulus presented, the late components of the averaged VEP waveforms (N200, P300, LN and LP) evinced significant amplitude differences across task conditions. These late components are termed event-related potentials (ERPs). For example, the amplitude of the P300 component of the waveform was much greater in amplitude in association with the Relevant stimulus (Blue) than with Red and Green stimuli, in particular at occipital and parietal locations, including Pz in Figure 1A,B (blue indicates Relevant, green and red lines indicate no response of Irrelevant). In addition, a differentiation of early and late potentials, mostly centered in the frontal region of the head (Fz) at 700 msec, was observed in both males and females in response to the Relevant stimulus as shown in Figure 1C,D.

We termed this P700 potential as the late positive (LP). Figure 1E,F compares the percentile distribution of ERP peak-to-peak amplitudes and latencies obtained at electrode Pz (N200, P300, LN) and Fz (LP) in male and female controls only (n = 24,22, respectively).



Note: Insets show the Red, Green and Blue stimuli that were randomly presented at 2-4 sec intervals. Subjects responded to the Relevant stimulus (i.e., Blue). (A,B) These graphs show grand-averaged VEPs recorded in male and female subjects at electrode Pz in response to Red, Green and Blue stimuli. The vertical scales are normalized to facilitate comparisons between gender. Reaction time (RT) is shown to the Relevant stimulus by arrow. (C,D) These graphs show grand-averaged VEPs recorded in male and female subjects at electrode Fz in response to Red, Green and Blue stimuli. The components of the VEP at Fz included the LP. Reaction time (RT) is shown to the Relevant stimulus (i.e., Blue). (E,F) Summary of descriptive statistics (i.e., 10-90% range, median, 2nd and 3rd quartiles) of N50-LP amplitudes and latencies obtained at Pz (N200, P300, and LN) and Fz (LP) for the Relevant stimulus in male (M) and female (F) subjects in this task.

Figure 1. Gender differences in VEP and ERP amplitudes and latencies recorded at electrode site Pz and evoked in the color recognition task.



Note: Insets show the Red, Green and Blue stimuli that were randomly presented at 2-4 sec intervals. Subjects responded to the Relevant stimulus (i.e., Blue). (A) The topomaps (circles) represent grand averaged potentials in male subjects on the head before (PRE), and at 189 msec (N100), 349 msec (P300), and 699 msec (LP) after the presentation of the color stimuli. The color map scales are normalized to facilitate comparisons between gender for control subjects in this figure. The top of each circle is the front of the head and the bottom of each circle represents the back of the head, as if looking down on the head from above. Violet represents extreme negative potentials and red represents extreme positive potentials. The pre-stimulus maps show no recordable activity before the stimulus. Note the differentiation of the P300 and LP ERPs associated with the Relevant stimulus in males. (B) These topomaps are grand averaged female responses normalized to the color scale for males. Note that females have a less prominent distribution of ERPs than males.

Figure 2. Gender differences in the distribution of VEP and ERP mapping in the color recognition task.

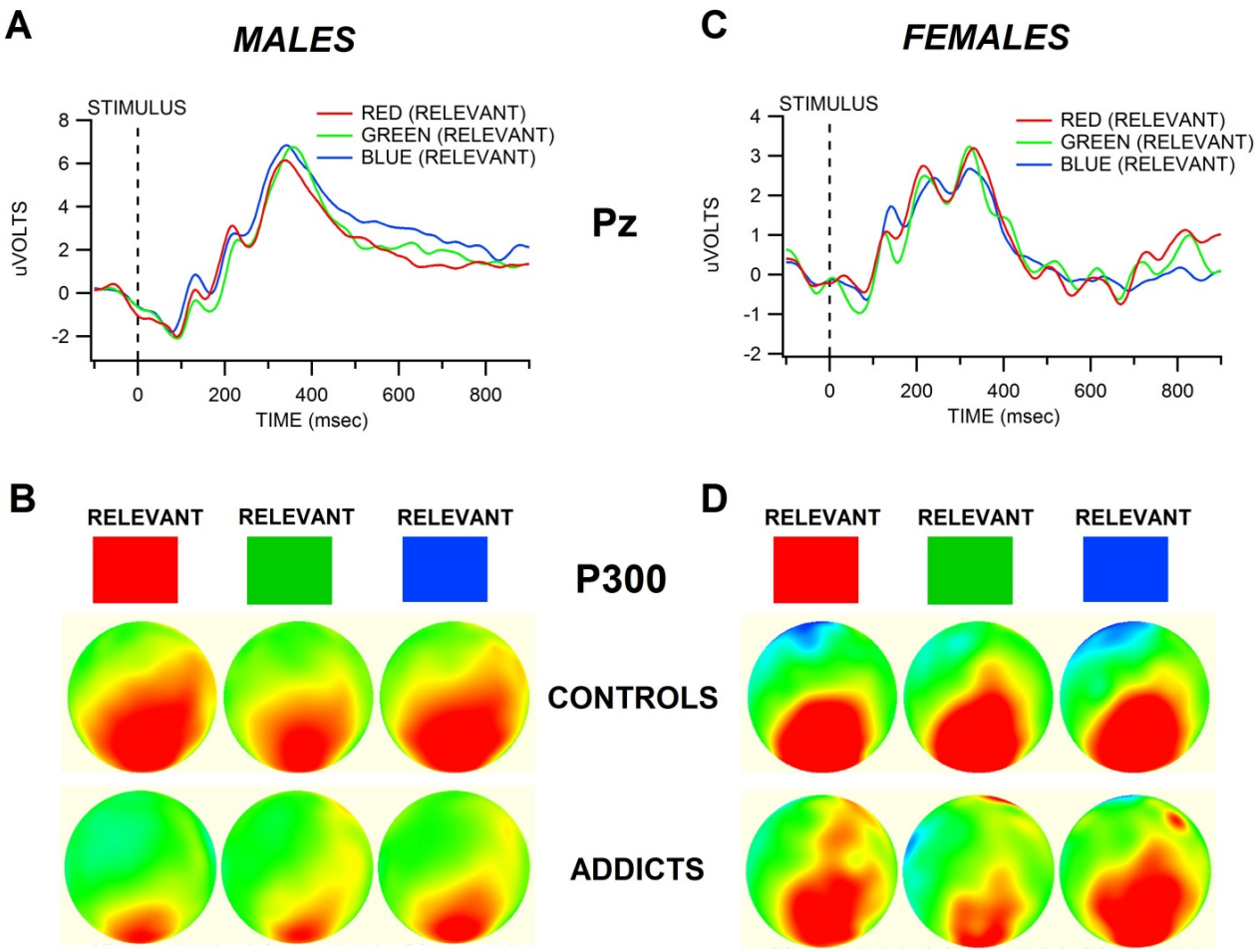
The EGI 128 electrode system enabled visualization of potentials over the head termed "topomaps" at a designated window of time before and after the visual stimulus. As shown in Figure 2, grand-averaged topomaps were obtained in male and female subjects before and after the presentation of color stimuli. P300s were localized mostly to the back of the head and late positives (LPs) mostly to the front of the head in association with the Relevant stimulus.

Compared to male control subjects, P300s and LPs in female controls were less prominent (n = 24,22 respectively).

H_1) – Results Summary (continued): Gender Differences in Visual-evoked and Event-related Potentials in the Color Recognition Task: Effects of Wavelength

Robust ERPs were obtained in all male and female subjects (including addiction group; 40 males, 35 females) in the color Go/NoGo task. Given the role of blue color processing in dopamine (DA)-associated disorders, we wanted to determine if color wavelength was a factor. Thus, in the current study, we also evaluated the effects of Red and Green color presentations when Relevant stimuli in the same Go/NoGo task as we did when Blue was the Relevant stimulus.

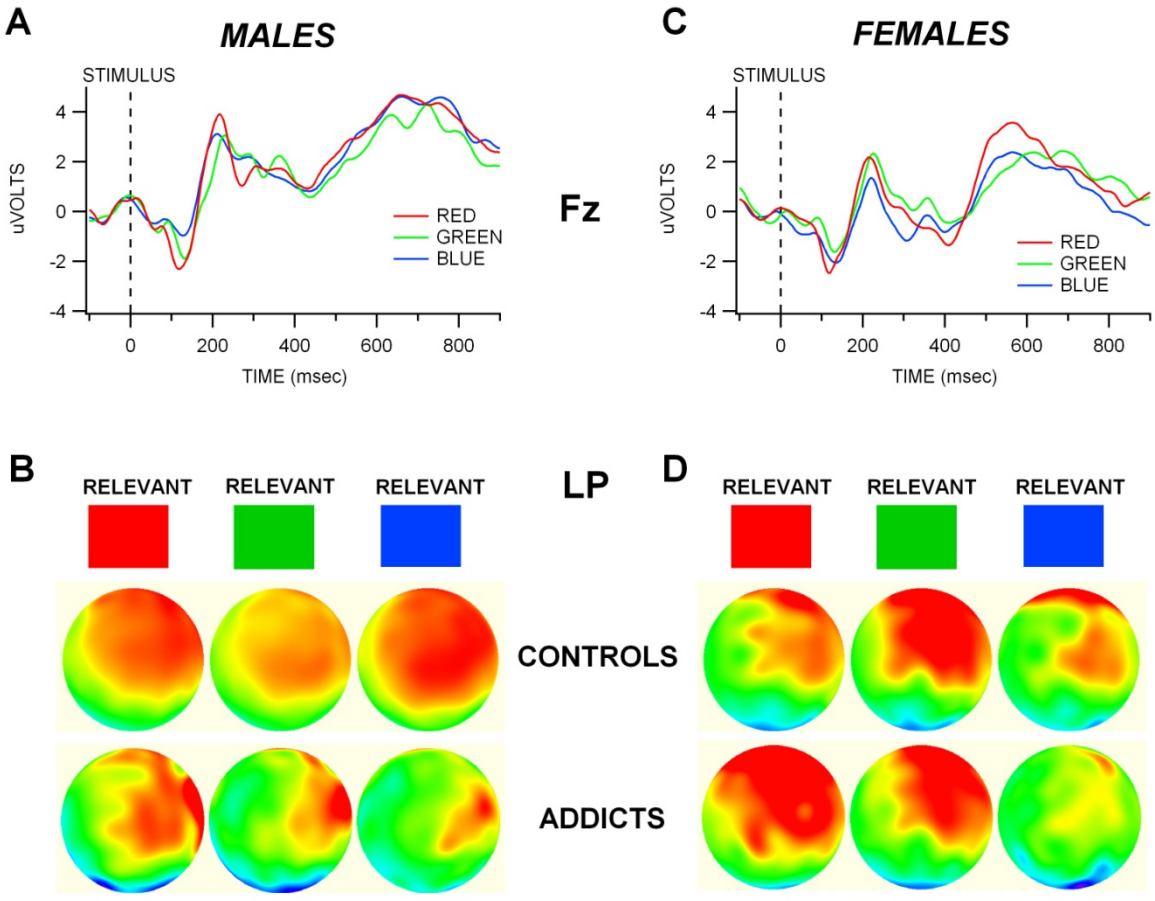
Figure 3 shows superimposed grand-averaged waveforms (Figures 3A,C) and topomaps (Figures 3B,D) obtained at Pz at 349 msec for Red, Green and Blue as Relevant stimuli in male and female subjects (for both addiction and control condition). It should be noted that the vertical scales are NOT normalized in order to compare Relevant responses for Red, Green and Blue within gender. There was no significant differences within groups in P300s when Red, Green or Blue were the Relevant stimulus.



Note: Subjects responded to the Relevant stimulus for each of the wavelengths Red, Green and Blue in separate Go/NoGo experiments. The vertical scales and color maps are NOT normalized in order to compare Relevant responses for Red, Green and Blue within gender. (A,B) There was no effect of wavelength on P300s in the grand-averaged VEPs at Pz or the distribution of potentials on the topomaps corresponding to P300 (i.e., 349 msec) in male subjects. (C,D) There was no effect of wavelength on P300 at Pz or the distribution of potentials on the topomaps in female subjects.

Figure 3. Effects of wavelength on P300s in male and female subjects in the color recognition task.

Figure 4 shows superimposed grand-averaged waveforms and topomaps obtained at Fz at 699 msec for Red, Green and Blue as separate Relevant stimuli in male and female subjects. There was no significant difference in LPs between Red, Green or Blue as Relevant stimuli (n=24 for males and n=22 females).



Note: All subjects responded to the Relevant stimulus for each of the wavelengths Red, Green and Blue in separate Go/NoGo experiments. The vertical scales and color maps are NOT normalized in order to compare Relevant responses for Red, Green and Blue within gender. (A,B) There was no effect of wavelength on LPs in the grand-averaged VEPs at Fz or the distribution of potentials on the topomaps corresponding to LP (i.e., 699 msec) in male subjects. (C,D) There appears to an effect of wavelength on LP at Fz or the distribution of potentials on the topomaps in female subjects particularly in the female addicts.

Figure 4. Effects of wavelength on LPs in male and female subjects in the color recognition task.

Hypotheses Two (H_2)

H_2) *There will be sex differences in ERPs in opiate addicts for simple go-nogo task in visual color processing tasks, particularly in the processing of the color blue.*

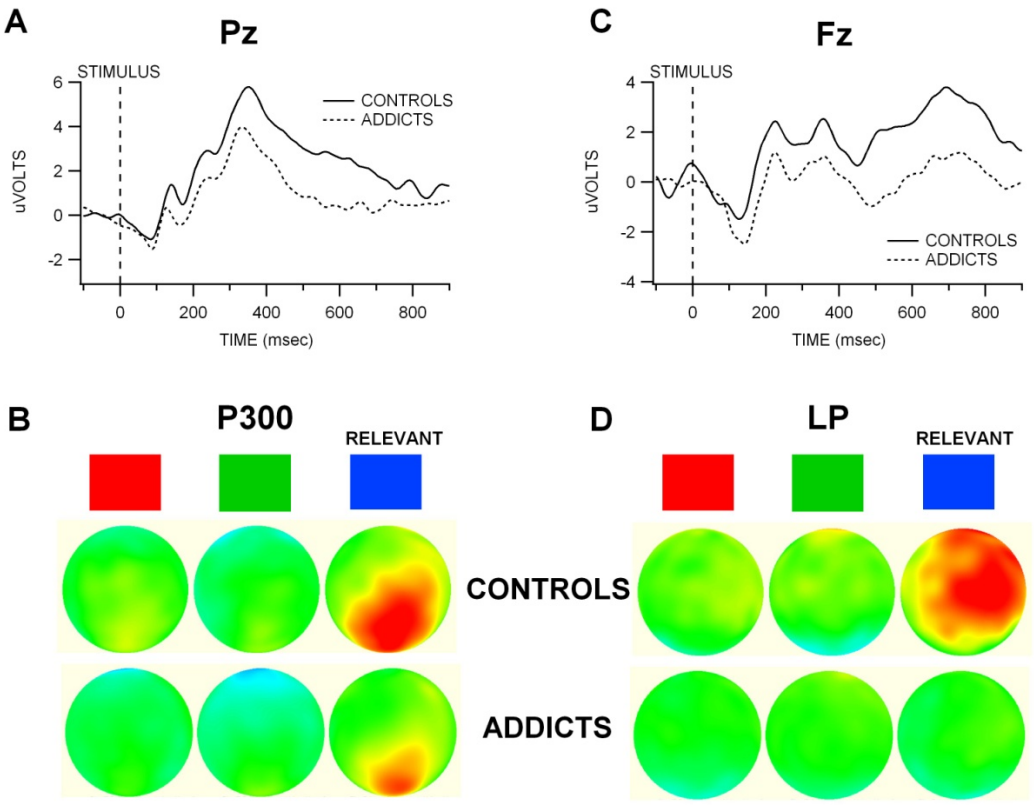
Hypothesis Three (H_3)

H_3) *There will be differences in ERPs between drug-free controls and opiate addicts for visual color processing tasks, in particular ERP differences in the processing of the color blue.*

Results Summary

Addiction Differences in Event-related Potentials in the Color Recognition Task

Based on grand-averaged VEPs and topomaps, there appeared to be important gender differences in the color recognition task (revisit Figures 1 and 2). Mainly, males were typically characterized by larger P300 and LP ERPs on the waveforms. One of the main objectives of this study was to evaluate cognitive processing in opioid addicts. Thus, we first compared ERPs in controls vs addicts in the color recognition task in all subjects, irrespective of gender. Based on grand-average VEPs and topomaps, Figure 5 shows that addicts were characterized by smaller P300s (Figure 5A,B) and LPs (Figure 5C,D) than in controls.

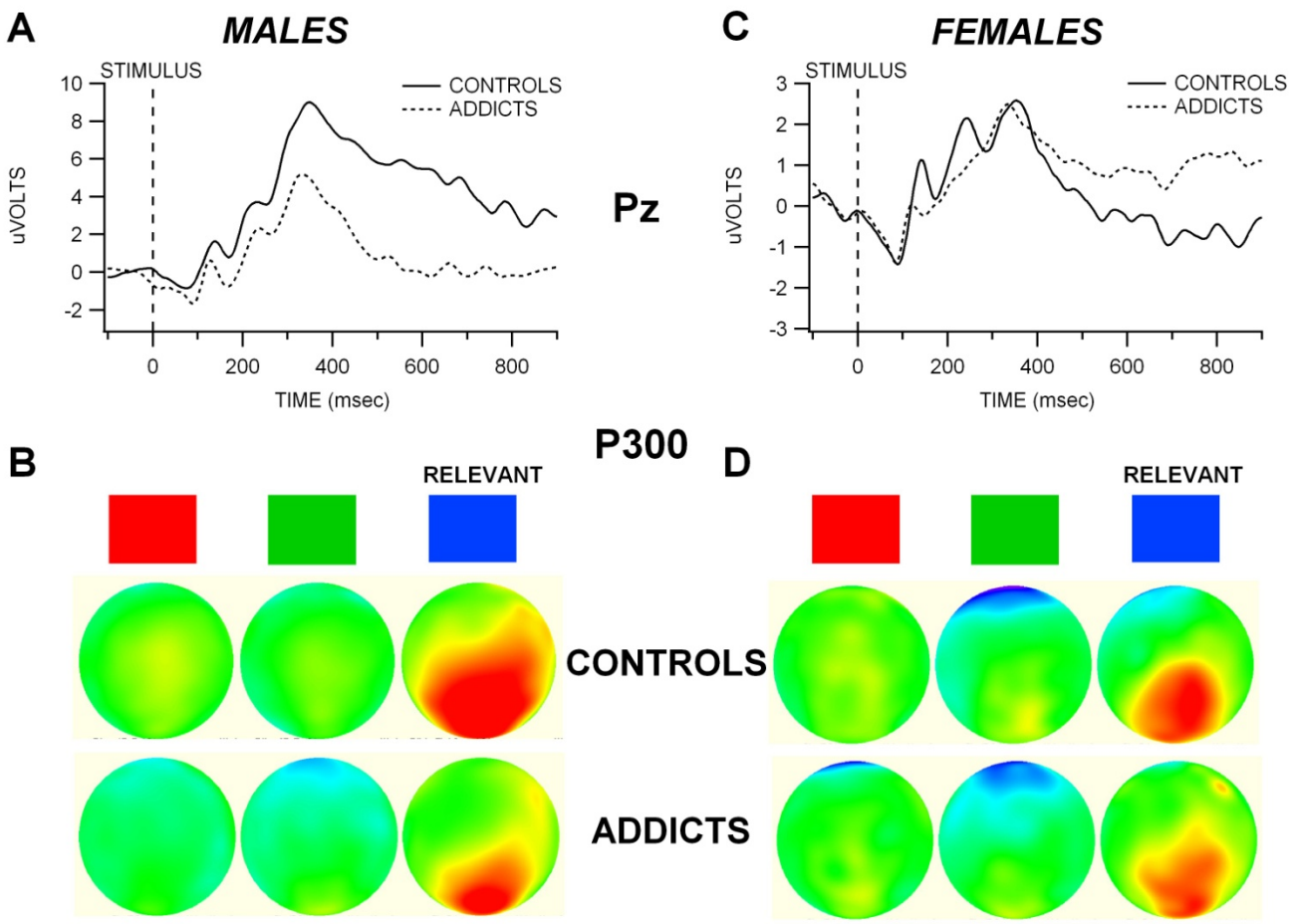


Note: (A,B) Compared to controls, addicts were characterized by smaller P300s on the grand-averaged waveform (Relevant stimulus only shown) and topomaps at 349 msec (P300). (C,D) Addicts were also characterized by markedly reduced LPs both on grand-averaged VEP waveforms and on the topomaps at 699 msec (LP).

Figure 5. Effects of addiction on P300s and LPs in the color recognition task.

Effects of Gender and Addiction on P300s in the Color Recognition Task

Figure 6 compares grand-averaged VEPs obtained at the Pz site and topomaps of the P300 in controls vs addicts by gender. While male addicts appeared to have significantly smaller P300s than male control subjects (Figure 6A,B), the P300s in female addicts did not appear to be significantly different from female controls (Figure 6C,D).

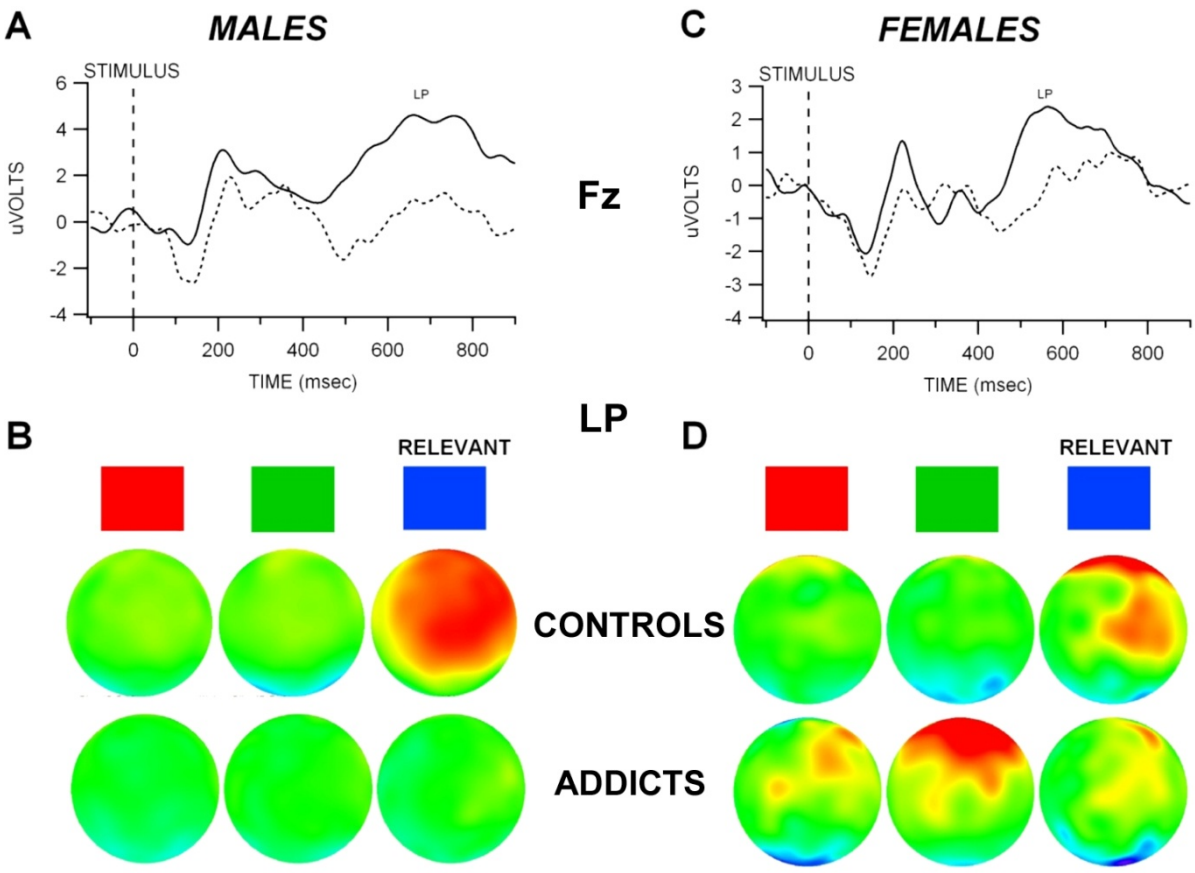


Note: (A,B) Compared to controls, male addicts were characterized by smaller P300s on the grand-averaged waveform (Relevant stimulus only shown) and topomaps at 349 msec. (C,D) P300s in female addicts did not appear to be different from female controls.

Figure 6. Effects of gender and addiction on P300s in the color recognition task.

Effects of Gender and Addiction on LPs in the Color Recognition Task

Figure 7 compares grand-averaged VEPs obtained at the Fz site and topomaps of the LP in controls vs addicts by gender. Male addicts appeared to have smaller LPs than control subjects (Figure 7A,B). Female addicts also appeared to have smaller LPs than control subjects. (Figure 7C,D).



Note: (A,B) Compared to controls, male addicts were characterized by smaller LPs on the grand-averaged waveform (Relevant stimulus only shown) and topomaps at 699 msec. (C,D) LPs in female addicts were also smaller, but with complexities to the Irrelevant stimuli.

Figure 7. Effects of gender and addiction on LPs in the color recognition task.

H_2 and H_3 Results Summary (continued)

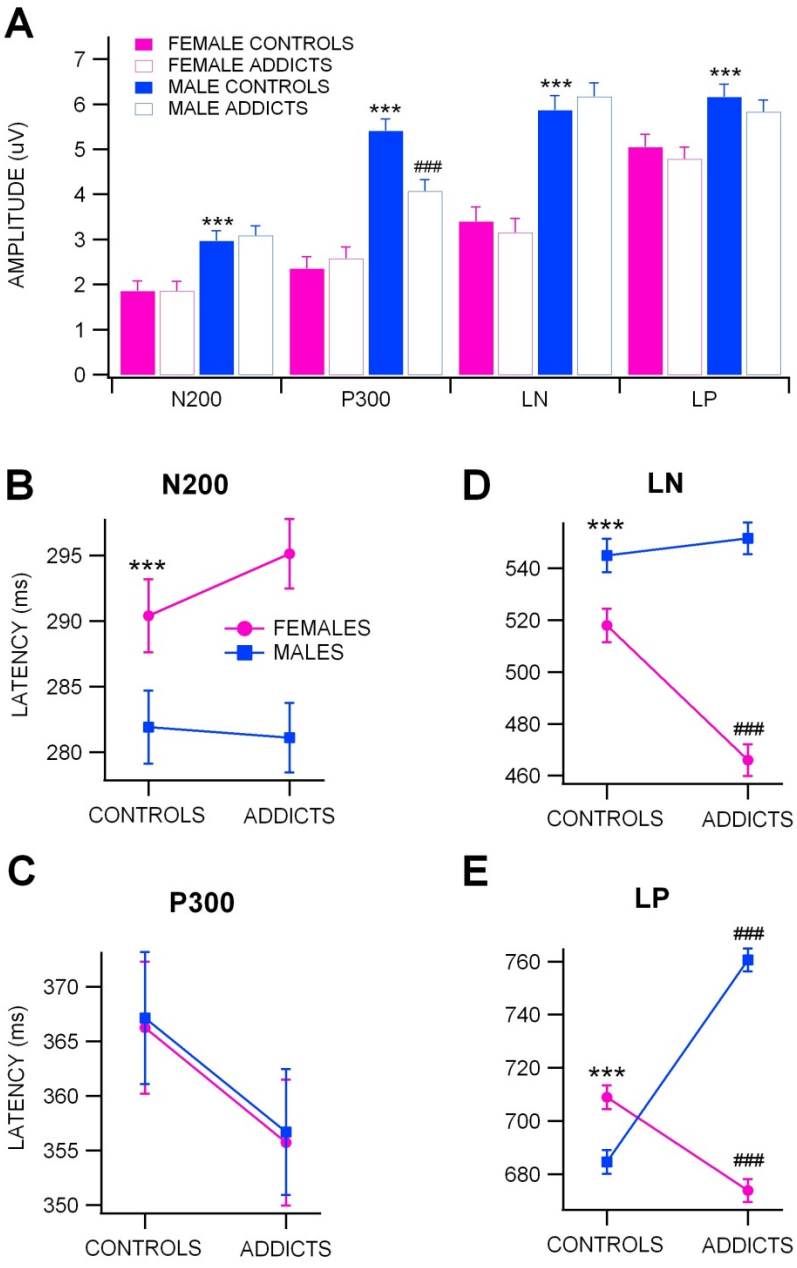
Addiction Differences in the Amplitude and Latency of Event-related Potentials in the Color Recognition Task

While the grand-averaged VEPs and topomaps demonstrated differences between responses obtained with the Relevant stimulus, averaging often underestimates the significance of the effects due to temporal dispersion and other vagaries. Thus, we measured each component of the VEP and obtained individual measurements in each subject. These measurements were

then submitted to statistical analysis. The independent variables were gender, 18 electrode locations of the 10-20 System and stimulus condition (e.g., Relevant), while the dependent variables were each of the VEP components.

As shown in the methods, to simplify the analysis, we consolidated the 18 electrodes into groups of anterior, central, and posterior or front, middle and back electrode locations on the head. We chose to evaluate averaged posterior electrodes of the 10-20 International electrode system (T5, P3, Pz, P4, T6, O1 and O2) for measurements of N200, P300 and LN and averaged posterior electrodes (FP1, FP2, F7, F3, Fz, F4, and F8) for measurements of LP (See Appendix C for International 10-20 montage). For each subject, measurements were extracted at windowed latencies corresponding to each of the ERPs. Figure 8 summarizes with a bar graph the gender and addiction effects on ERP (N200-LP) amplitude and latency in the color recognition task. Compared to females, males were characterized by significantly greater N200, P300, LN and LP amplitudes (Figure 8A).

Compared to male controls, addicts were characterized by significantly lower P300 amplitude (Figure 8A). However, female addicts did not show any significant ERP amplitude reduction. Figures 8B,E summarize the gender and addiction effects on ERP (N200-LP) latencies in the color recognition task. Males were characterized by significantly shorter N200 and LP latencies and significantly longer LN latencies compared to females. Compared to male controls, opiate addicts were characterized by significantly slower LP latencies. Compared to female controls, opiate addicts were characterized by significantly faster LN and LP latencies. (Table 2 shows F and P values for each of the ERP amplitudes and latency by contrasts evaluated by gender and by addiction in the current study.)



Note: (8A) This graph summarizes ERP amplitude measurements in males and females and addicts. Males had significantly greater N200, P300, LN and LP amplitudes compared to females. Only male addict P300 amplitudes were significantly lower than controls. Asterisks *** represent significance values P<0.001 between gender, respectively. Symbols ### represent significance values P<0.001 between controls and addicts.

Figure 8. Gender and addiction differences in the amplitude and latency of event-related potentials in the color recognition task.

Table 2

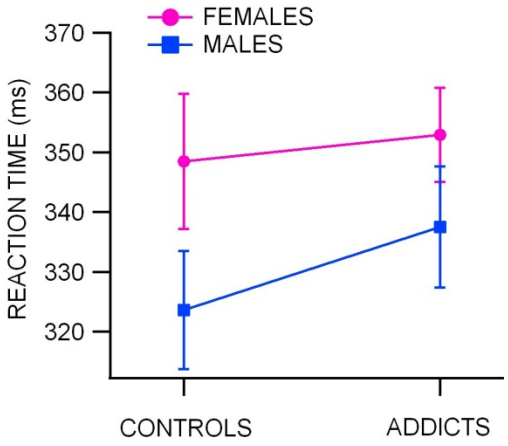
Effects of Gender and Addiction on ERP Amplitude and Latency in the Color Recognition Task

		AMP		LAT	
ERP	Contrasts	*F*	*p*	*F*	*p*
N200	male vs female controls	51.8	<0.0001***	96.33	<0.0001***
	controls vs addicts	0.94	0.33	5.1	0.02*
	male controls vs male addicts	4.62	0.03*	6.7	0.01*
	female controls vs female addicts	0.44	0.5	0.47	0.49
P300	male vs female controls	123.2	<0.0001***	2.3	0.13
	controls vs addicts	2.61	0.11	1.15	0.29
	male controls vs male addicts	8.95	0.003**	5.5	0.02*
	female controls vs female addicts	0.3	0.57	0.5	0.48
LN	male vs female controls	131.7	<0.0001***	142.7	<0.0001***
	controls vs addicts	0.31	0.58	54.3	<0.0001***
	male controls vs male addicts	3.3	0.07	5.1	0.02*
	female controls vs female addicts	0.85	0.36	63.0	<0.0001***
LP	male vs female controls	58.1	<0.0001***	43.2	<0.0001***
	controls vs addicts	2.3	0.13	39.4	<0.0001***
	male controls vs male addicts	1.92	0.17	288.25	<0.0001***
	female controls vs female addicts	0.59	0.44	50.7	<0.0001***

Note: ERP = event-related potentials; AMP = amplitude; LAT = latency;
Degrees of freedom for all values = 450, *p <.05. **p < .001. ***p < .0001.

Effects of Gender and Addiction on Reaction Time (RT) in the Color Recognition Task

Figure 9 compares reaction times (RTs) in males and females and in controls vs addicts. Reaction time was determined from the time of stimulus presentation to the time subjects responded with a key press to the Relevant stimulus. In the color recognition task, there was no significant difference between males and females ($p > 0.05$; n = 40,35) nor between male controls and male addicts ($p > 0.05$; n = 24,16) or female controls and female addicts ($p > 0.05$; n = 22,13).



Note: There were no significant differences between males and females or between controls vs addicts by gender.

Figure 9. Summary of reaction time comparisons between males and females and addicts within gender.

CHAPTER 5

Discussion

The primary hypothesis of the current study was that visual processing differ significantly between males and females. It was further hypothesized that blue color processing, which is regulated by the neurotransmitter dopamine (DA) in the retina reflecting dopamine neurotransmission implicated in drug and natural reward in the mesolimbic system, could be hypothetically viewed through EEG amplitudes and latencies as a biological DA neurotransmission marker of the addictive state in males and females. It was anticipated that the sex differences previously found in a visual object recognition task would be replicated when associated with blue color processing in the visual system and there would be similar EEG amplitudes and latency differences found in male and female substance abusers while visually processing the color blue.

Current Study

For the current study, color processing appears to be very gender sensitive and perhaps stimulus-selective (i.e., Blue color evoked a P300 while Irrelevant Red or Irrelevant Green did not in the Go/NoGo task). Indications are that the color recognition task was good in that we were able to differentiate distinct amplitudes and latencies across all components with initial observations. As hypothesized, there were significant gender differences found in visual evoked potentials (VEPs) and subsequent event related potentials (ERPs) from the color recognition task in that male controls had greater P300 and LP ERPs than female controls—a similar gender difference was also seen in the opiate addiction cohort as hypothesized. In addition, indications

of wavelength differences for the color blue as hypothesized may be relevant for increases or decreases in retinal (DA) neurotransmission, were found—no significant gender differences were found early at Pz P300 for addiction or gender, but there were significant LP differences in the addiction group for both gender and addiction. As hypothesized, there were gender and addiction ERP differences in amplitudes and latencies for N200, P300, late negative (LN) and LP—males and females differed significantly in all and male addicts had significantly lower P300 than male controls but not females.

In the current study, the color recognition task appears to be highly relevant particularly as a gender-selective physiological measure. It also has strong indications as a way to check for retinal DA neurotransmission differences for both within gender and opiate addiction. The marked gender differences found in this color recognition task, when comparing within subjects and across groups, may provide us with a powerful tool to studying DA-dependent processes in male and female controls and in males and females struggling with opiate addiction.

General Discussion of ERP Amplitude Data

N100 and N200. Although they were not part of the original scope of the current study, the high levels of N2 amplitudes in the male cohort should be addressed because of recent phenotype studies in addiction (Archibald, et al., 2009; Begleiter & Porjesz, 2006; Iacono, et al., 2000; Iacono, et al., 2003; Kamarajan, et al., 2005; Porjesz et al., 2002; Porjesz & Rangaswamy, 2007). High amplitudes in male controls were observed versus much lower ones in female controls (i.e., these amplitudes were very unusual looking – almost like there wasn't a P300) and yet there were no significant differences between the female groups. In an effort to see if there was an ERP, the noise ratio was lowered to 7/2 and we were able to distinguish small ERPs for both female groups. The N200 differences may reflect the high readiness, arousal or anticipation

in males for an oddball task which reflects the findings of other studies (Treisman, 1994; Wolfe, 2003). It is possible that the females do not necessarily have a decreased amplitude since their latencies are very similar to the males rather than those found in substance abuse cohort; therefore it was important to look at the amplitude within groups and between groups in this particular task – in particular for different biological retinal development and possible differences in DA neurotransmission as the current study suggests (Elkashef & Vocci, 2003). These would be sex differences specific to activation of the reward system and what drives it. For example, it is possible that females have a system favoring the fusiform area and find face recognition a more rewarding behavior (Oliver-Rodriguez, et al., 1999) while males may be more genetically predisposed to parietal tissue involvement as seen in an oddball task (Olbrich, et al., 2000).

Attraction to moving or different pop-out stimuli as discussed by Kovalick (2008) to teachers in a discussion of differences in phenotypical type behaviors of girls and boys in the classroom setting may be another explanation for such pronounced differences of generation in neuronal synaptic activity in these simple tasks in controls (Bigler & Fleming, 1976; Elkashef & Vocci, 2003; Iacono, et al., 2000; Muller, Kuhn, Buttner, & Przuntek, 1999; Putnam et al., 2005).

Another possibility is an increased amount of the dopamine (DA) sending ganglion cells found in the male retina; male retinas have mostly the larger, thicker M (magnocellular) ganglion cells that can track objects anywhere in the field of vision (Vaegan & Hollows, 2006). Very little is known about sex differences in the retina and differences in DA production as indicated in the current study.

P300. Speaking to the findings of the current study, the data collected from the color recognition study were consistent with the hypotheses that male and female ERPs would be

different and, as seen in the descriptive data summaries they are different across all amplitudes for N200, P300, LN, and LP.

The significant sex differences for opiate addiction within females and opiate addiction within males indicates that the groups are different from each other and match the literature regarding reduced amplitude in P300 for male alcohol and cocaine addicts when compared to male controls (Bauer & Hesselbrock, 2003; Emmerson, et al., 1987; Pandey, et al., 2012)—little has been said in the literature about females and addiction until recently (Green, et al., 2009) especially regarding P300. In addition there are few ERP studies of cognitive processing involving use of the color blue as a stimulus, however, Ikegami, Takano, Saeki and Kansaku (2011) recently found that controls and a group with cervical spinal cord injury both performed more accurately on blue/green flicker matrices than white/gray on a P300-based brain computer interface (BCI). The current study was designed to address that. We have recently found that P300s do not vary across the menstrual phase, suggesting cycle cannot account for difference between males and females (Nash, 2009; Wolf, 2012).

The gender differences in the color discrimination task are substantial. With such significant sex differences between controls and the male addicts and male controls, and no female differences found within addiction (only at the Fz LP at increased noise ratio) warrants continued extensive observation. The reaction time (RT) for this task being so close to the stimulus is also very marked and interesting with literature showing that such RT changes suggest possible disturbance in inhibitory function such as that seen in patients with schizophrenia (Bahramali et al., 1998) or other brain diseases or disorders. In addition, consideration of such things as photosensitivity and the photic stimulation of computer monitors and possible motor disinhibition in those who do not have epilepsy (Takahashi et al., 2001) is

warranted. Reflex seizure can happen from simple flashing displays in those who are sleep deprived, or have had prolonged exposure to video games or have used drugs or alcohol (Zifkin & Inoue, 2004). Conversely, a recent study showed that reaction time increased if there was no cognitive access to the meaning of a word flashed on the screen (Dionisie & Luca, 2011). It is also possible that the fact the colors and word matches were easily matched by all participants involved, this would allow for increased speed of processing reaction time.

Late positive (LP). The obvious differences in opiate addiction for late positive amplitude for this color task is similar to that found regarding sex differences in face processing (Oliver-Rodriguez, et al., 1999) and in processing unpleasant stimuli (i.e., spiders) as seen in Brown et al. (2012) with an all female cohort. It would be interesting to extend this study to include and compare male LPs.

Latencies. While there were significant ERP amplitude gender differences for controls across several components observed in the current study, there were significant differences in amplitude were marked in addiction and gender for the LP. In one color ERP and latency study (a green vs red visual test for reaction time) looked at the impact of psychological stress (Venkatesh, Ramachandra, Baboo, & Rajan, 2002), suggesting that longer reaction time found for females could be due to sex hormones which may reduce velocity of nerve impulse and increase synaptic delay—they also postulated that the color green evoked a faster response from greater stimulus on visual receptors. Such was not found with wavelength changes in the current study but a similar LP decrease in latency was found in addicts irrespective of gender.

Potential Limitations and Problems

Potential limitations may come from the smaller sample size for the addiction group than the controls. Traditionally very few of the EEG studies of substance abuse have reported large

sample sizes; this may be due to the stigma of substance abuse and addiction. Further, similar significant gender differences for the control group in the color discrimination task were found, allowing for increased reliability of the results in the smaller clinical group. Another confound comes from the paucity of EEG research specific to opiate dependence (Attou, et al., 2001) and color processing (Desai, et al., 1997; Roy, et al., 2003; Roy, Roy, Smelson, et al., 1997; Roy, Roy, Williams, et al., 1997; Roy, Smelson, et al., 1997) for designing our experiment to replicate or follow (see Luck, 2005 for common errors in electrophysiological experiments). However, this study does have similar results to those of alcohol and cocaine abuse studies with decreased P300 amplitudes and increased latencies found in the opiate addiction group.

Further, the fact the addicts were in withdrawal and active detoxification may limit our results in regards to the effects of "kindling" or hypersensitivity of the limbic system as seen in chronic alcohol withdrawals (Ballenger & Post, 1978; Smookler & Buckley, 1970), nevertheless our findings did match the literature for changes in ERP data with chronic drug use and alcohol and detoxification (Gonzalez, et al., 2004; Kouri, et al., 1996; Lubman, et al., 2009; Rich, et al., 2005). Similar decreased P300 amplitudes and increased latencies related to disinhibition maintained across time (as seen in alcoholism and other chronic drug use) were found. This also correlates with the current treatment dogma that encourages substance abusers and those addicted in early abstinence or the withdrawal period to avoid their former drug-use places, friends, relationships, etc.; any "triggers" or "cues" for former drug use that can lead to disinhibition and to relapse.

Finally, self-report in substance abuse can be a problem, but most substance abuse research must rely on such to complete their studies and literature indicates that for the most part

it has been found to be reliable (Attou, et al., 2001; Coviello, et al., 2004; Douglas et al., 2003; Kouri, et al., 1996; Murphy, et al., 2010; Turk, et al., 2008).

Future Studies

As DA is considered one of the greatest driving forces in substance abuse as indicated by biological research over the past decade I believe that there should be a continuation of the current study that looks at DA levels matched with different tasks and EEG/ERP studies. An increase of sample size and comparison with other neuroimaging techniques would be in line using different types of stimuli would be appropriate. Also, another way to sample for DA depletion would be in order using the same color recognition task.

In view of the findings of recent sex differences studies for object recognition tasks (Nash, 2009; Steffensen, Ohran, et al., 2008; Wolf, 2011), there needs to be an increase in the consideration of possible hormonal effects on DA neurotransmission in males and females, including those associated with all types of addiction or other disinhibitory disorders (White & Kalivas, 1998). Of great interest is the recent very large study (almost 30,000 assessments from 220 treatment centers collected from 2005-2008) showing significant differences in male and female *opioid* use (Green, et al., 2009), with women out-using the men but not for opiate or heroin use (Wise & Hoffman, 1992) and especially when women were already problem drinkers. This has significant implications for prescribing of opioids for pain for women who appear to be more at risk for abuse (Buckley, Calvert, Lapidus, & Morris, 2010; Chou, et al., 2009; Coviello, et al., 2004; Fishbein, et al., 2007; Iacono, et al., 2003; Webster & Webster, 2005).

In addition, consideration of a simple, cost effective visual processing test that could recognize signs of relapse or risks for abuse if use begins, from compromised ERP or VEPs are necessary, along with the possible development of some type of light visualization (Pascoli,

Turiault, & Luscher, 2012; Wolf, 2012) or other environmental enhancement stimuli that works in improving the inhibition systems as are being studied in cocaine addiction reversal (Chauvet, Lardeux, Jaber, & Solinas, 2011; Pascoli, et al., 2012; Smookler & Buckley, 1970; Wolf, 2012). Similar research should be considered with opioid addiction given the recent world-wide reports of opioid misuse and abuse overtaking that of cocaine.

As Gazzaninga (2011) points out about neuroscience—we are just beginning to know who and/or what is in charge regarding "free will" in the human condition and what control we may have in neurobiology adaptation either way as it relates to our cognitive processing especially as it relates to substance abuse and addiction of any kind.

Questions such as: "Why can't they just stop?" in any kind of substance abuse and addiction need to continue to be asked and evidence-based answers need to be given with a firm foundation of understanding human behavior from a cognitive neuroscience foundation.

Conclusion

In conclusion, the results of this study indicate that there are visual attention, color processing and physiological measure differences in males and females with substance abuse and opiate addiction as hypothesized. There is also evidence that the color discrimination task used in the current study is sensitive to those differences and may be helpful in better understanding the biological underpinnings of opiate addiction and the disinhibitory behaviors associated with it—ones that may be associated with "out the gate" immediate, evoked potentials from visual stimuli that triggers some type of neurobiological cascade of neurotransmitters and component generation that can be "visualized" on EEG studies. The may lead to relapse in those trying to stimulate the reward system with or without thinking about it—in both females and males but particularly in males. There is further evidence that continued research in the area of DA

neurotransmission and looking for bio-markers in the visual system for opiate relapse as measured by EEG is warranted.

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APPENDIX A

DSM-IV and Proposed DSM-V Revisions

Part 1: Diagnostic Statistical Manual-IV Criteria for Substance abuse and Addiction and Substance Abuse: Seen as two disorders (American Psychiatric Association, 1994)

A. The 1994 DSM-IV diagnostic criteria for *Substance Abuse* is defined as:

A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by one (or more) of the following, occurring within a 12-month period:

1. Recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (i.e. repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household).
2. Recurrent substance use in situations in which it is physically hazardous (i.e. driving an automobile or operating a machine when impaired by substance use).
3. Recurrent substance-related legal problems (i.e. arrests for substance -related disorderly conduct).
4. Continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance

(i.e. arguments with spouse about consequences of intoxication, physical fights).

5. Absence of dependence has been established. (p.183).

B. The 1994 DSM-IV diagnostic criteria for *Addiction or Substance Dependence* is defined as:

A maladaptive pattern of substance use, leading to clinically significant impairment or distress, as manifested by three (or more) of the following, occurring at any time in the same 12-month period:

1. tolerance as defined by either of the following:

   (a) The need for markedly increased amounts of the substance to achieve intoxication or the desired effect; or

   (b) A markedly diminished effect with continued use of the same amount of the substance.

2. withdrawal, as manifested by either of the following:

   (a) The characteristic withdrawal syndrome for the substance; or

   (b) The same (or closely related) substance is taken to relieve or avoid withdrawal symptoms.

3. substance is often taken in larger amounts or over a longer period of time than intended.

4. there is a persistent desire or unsuccessful efforts to cut down or control substance use.

5. a great deal of time is spent in activities necessary to obtain the substance, use the substance or recover from its effects.

6. important social, occupational, or recreational activities are given up or reduced because of use.'

7. the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the use (i.e. continued drinking despite recognition that an ulcer was made worse by alcohol consumption). (p. 181).

Part 2: Proposed revisions by the American Psychiatry Association for 5th Edition of the Diagnostic Statistical Manual for Opioid Abuse and Opioid Dependence.

See http://www.dsm5.org/ProposedRevisions/Pages/proposedrevision.aspx?rid=315#

A. A maladaptive pattern of substance use leading to clinically significant impairment or distress, as manifested by 2 (or more) of the following, occurring within a 12-month period:

- recurrent substance use resulting in a failure to fulfill major role obligations at work, school, or home (e.g., repeated absences or poor work performance related to substance use; substance-related absences, suspensions, or expulsions from school; neglect of children or household)
- recurrent substance use in situations in which it is physically hazardous (e.g., driving an automobile or operating a machine when impaired by substance use)

- continued substance use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of the substance (e.g., arguments with spouse about consequences of intoxication, physical fights)
- tolerance, as defined by either of the following:

a. a need for markedly increased amounts of the substance to achieve intoxication or desired effect

b. markedly diminished effect with continued use of the same amount of the substance

(Note: Tolerance is not counted for those taking medications under medical supervision such as analgesics, antidepressants, ant-anxiety medications or beta-blockers.)

- withdrawal, as manifested by either of the following:

a. the characteristic withdrawal syndrome for the substance (refer to Criteria A and B of the criteria sets for Withdrawal from the specific substances)

b. the same (or a closely related) substance is taken to relieve or avoid withdrawal symptoms

(Note: Withdrawal is not counted for those taking medications under medical supervision such as analgesics, antidepressants, anti-anxiety medications or beta-blockers.)

- the substance is often taken in larger amounts or over a longer period than was intended
- there is a persistent desire or unsuccessful efforts to cut down or control substance use
- a great deal of time is spent in activities necessary to obtain the substance, use the substance, or recover from its effects
- important social, occupational, or recreational activities are given up or reduced because of substance use

- the substance use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by the substance

- Craving or a strong desire or urge to use a specific substance.

Severity specifiers:

Moderate: 2-3 criteria positive

Severe: 4 or more criteria positive

Specify if:

With Physiological Dependence: evidence of tolerance or withdrawal (i.e., either Item 4 or 5 is present)

Without Physiological Dependence: no evidence of tolerance or withdrawal (i.e., neither Item 4 nor 5 is present)

Course specifiers (see text for definitions):

Early Full Remission

Early Partial Remission

Sustained Full Remission

Sustained Partial Remission

On Agonist Therapy

In a Controlled Environment

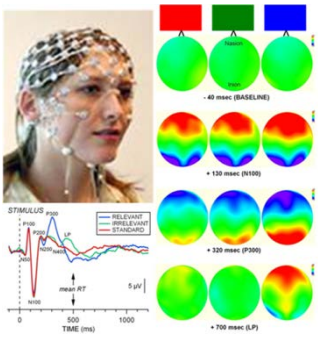
APPENDIX B

APPENDIX B1: Pre-Screen Checklist

BYU Addiction and Visual Color Processing Study
July - August 2011
Prescreening Checklist: Substance Abuse Research Subjects

PIs: Jo Ann Petrie, M.S. and Scott Steffensen, Ph.D.
Brigham Young University, Psychology Department and the Neuroscience Center
Title: "Visual attention, color processing and physiological measure differences in males and females with substance abuse and opiate addiction: Stage 3"

- ❒ 20 years to 40 years —either male (n = 6) or female (n = 6)
- ❒ **Not color-blind (if known)**
- ❒ Diagnosed with **opiate drug addiction** or dependence, (either legal or illegal; i.e., heroin, narcotic pain killers, methadone, OxyContin, Lortab, Percocet, hydrocodone; oxycodone; Suboxone, codeine, Fentanyl, morphine, Darvocet, Darvon, Lorcet, Vicodin, Tylox, Roxicet, etc., etc.; in other words **opiates are the drugs of choice** – participants can have used other drugs but prefer opiates – please no recent marijuana/spice use – it stays in system ~30 days)
- ❒ Experiencing withdrawal symptoms from none use for at least 24 hours but not longer than 60 days
- ❒ Still regularly (daily) "crave" or feel need for drug of choice
- ❒ No prior history of major brain trauma (e.g., severe blow to head, severe concussion, car accident with diagnosed brain injury)
- ❒ Seizure-free – no epilepsy
- ❒ No current use of anti-epileptic drug
- ❒ Not prone to fainting
- ❒ Not claustrophobic
- ❒ If taking medication for dual diagnosis – be willing to indicate on medical history sheet (see example attached)
- ❒ Willing to undergo:
  - 1 time EEG testing (electroencephalogram/brain imaging – see example at bottom)
  - Basic neuropsychological tests
  - UA (confidential – only PI(jp) will know results – data will be destroyed if +)
- ❒ Will be driven from treatment center to BYU campus for ~ 2 hour session – then returned to treatment center (approx. 3 ½ hours total)
- ❒ Will receive:
  - $20 Visa gift card
  - Given credit for 1 required meeting attendance



APPENDIX B2: Consent Forms

Visual Color Processing Differences in Males and Females with

Substance Abuse and Addiction

Consent to be a Substance Abuse Research Subject

Principal Investigator: Jo Ann Petrie, M.S.
Co-Investigator: Scott C. Steffensen, Ph.D.

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Introduction

This research study is being conducted by doctoral candidate Jo Ann Petrie, M.S. and Professor Scott C. Steffensen, Ph.D., at Brigham Young University to better understand sex differences in neural processing during the performance of computer tasks related to visual color processing in those with substance abuse and opiate addiction. You were invited to participate as a *substance abuse research subject* in this study because you are an adult who has been diagnosed with an addiction and who has expressed interest in participating in the study. We anticipate that about 60 people will participate in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Procedures

You will be designated to either the male or female group for study participation. Both groups will complete the same questionnaires and task procedures, with no differences in task instructions. All substance abuse participants will receive the same amount of compensation regardless of performance.

For all participants, the study consists of four main parts: 1) filling out an on-line questionnaire and a self –report of any medication/drugs used in past 4 months; 2) give a urine sample for drug analysis; 3) completing a manual color deficiency task and three basic neuropsychological tests, 4) completing computerized tasks while we measure with EEG the small amount of electrical activity that is produced by your body.

- On-line or computer generated questionnaire: Before the physiological measures are obtained, you will be asked to complete a questionnaire on-line including simple questions on your background (for example, your age and marital status);and a section on your medical history and your family's medical history, that is similar to questionnaires you may have filled out at a doctor's office. It should take only 10-15 minutes to complete this questionnaire.

- Medications Used Screening: You will be asked to list all medications that you are currently taking (including insulin, oral contraceptives, prescription medications, over-the-counter medications, vitamins, diet supplements, herbal supplements, etc.). This will be to determine whether or not your EEG data will be included in the drug-free control database.

- Urine Analysis (UA) Drug Screening Test: You will be asked to give a small urine sample for analysis to verify that your system is truly drug free for control purposes. You will be given a UA test jar that is identified only by the ID number associated with the other tests you are completing today. Before doing those other tests you will be shown to a restroom near to the EEG lab and given full privacy to complete the test. After following the instructions on the test kit you will place it in a secured box provided by the research assistant which will be collected later by the PI to be taken for drug analysis. You will then continue with all of the other tests as outlined. This data will be destroyed once the analysis report is completed and given to PI.

- Color Deficiency test: Administration of the *H.R.R. Pseudoisochromatic Plates* color vision test will take place. You will look at a series of color plates and respond both verbally and with a brush to what you see regarding symbols and shapes on the plates. Completion will take about 5 minutes.

- Neuropsychological tests. We will have you complete 3 standard neuropsychological tests looking for variability in visual, motor and cognitive processing speeds. These will take about 20 minutes.

- Computerized tasks: We will record the activity of your brain while you perform various computerized tasks that involve: 1) presentation of a Stroop effect test including presentations of words and colors in various ways on a computer monitor display requiring you to respond by pressing a keypad as quickly and accurately as possible; 2) responding to flashes of colors presented on the monitor; or 3) watch the monitor as the colors flash with no response. You will also be asked to respond to what numbers you see on the computer screen while wearing 3-D glasses – the same type worn in movie theaters. This is a test of binocular rivalry and you will have a practice session before you start the computer tests. We will measure brain-wave activity from 128 sensors placed on your scalp while you complete the task. The sensors for recording brain wave activity are both painless and harmless; they merely record the small electrical signals produced by your brain. The experimenter will clearly explain where these sensors will be placed before applying them. Completion of these tasks will take about 50 minutes.

Study participation will be completed within one session that will last no longer than 2 hours.

Risks/Discomforts

There are minimal risks for participation in this study. Questionnaires will ask you for information about some sensitive issues, such as your medical history and substance use and any family history of the same. If you are not comfortable answering these questions, you can choose not to answer and discontinue participation in the study. If we should discover, based on the questionnaires, that you experience marked depression or anxiety, we will offer to make an appropriate referral.

Electroencephalogram or EEG is what is used to measure the electrical ("brain wave") activity of your brain. The risks associated with EEG in this study do not differ from those associated with a standard clinical EEG. The primary risk involves the slight possibility of irritation at the site of sensor application. Every precaution is taken to prevent irritation, and sensors are cleaned and disinfected after each use. We also make an effort to use materials appropriate for sensitive skin.

You will be excluded from study participation if you have a history of *seizures, claustrophobia, fainting, or, brain trauma (i.e., blow to head, concussion, car accident with diagnosed brain injury)*. As mentioned above, the fitting of the electrode net may involve some discomfort to your scalp or even minor pain. You will be carefully monitored throughout the procedures and may stop participating at any time if you become uncomfortable.

Benefits

Please note that the data obtained will not be used for clinical purposes but simply for this research. That is, the data obtained will not be evaluated for the purposes of personal diagnosis or treatment of neurological disease, and this research procedure does not take the place of a clinical EEG procedure.

There are no expected direct benefits to you for participating in this study; however, there exists the possibility of incidental findings of clinical significance from the EEG. Should such findings emerge as a result of your participation we will recommend that you see a physician for an evaluation.

There are no expected direct benefits to subjects for participation in this study. However, it is hoped that through your participation researchers may learn more about gender differences in visual attention and color processing. Furthermore, it is believed that this information can be used in the future to assist researchers to better understand gender differences in identifying and determining treatment outcome measures in substance abuse or addicted patients.

Confidentiality

If you decide to participate in this study, the researcher will get information that identifies you and information about you. This may include information that might directly identify you, such as your name and age. The principal investigator will keep a link that identifies you to your coded information, but this link will be kept secure and available only to the investigator or selected members of the research team. **Any information that can identify you will remain confidential.** The research team will only give this coded information to other members of the research team to carry out this research study. This information will be kept for seven years. After that time it will be destroyed or de-identified, meaning we will replace your identifying information with a code that does not directly identify you.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Data are safeguarded in locked cabinets in locked offices, and electronic data are stored on password-protected computers. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the BYU Institutional Review Board (the Committee that reviews, approves, and monitors human subject research) may inspect study records during auditing procedures. However, these individuals are required to keep all information confidential.

Compensation

Substance Abuse participants: will receive a $20.00 Visa gift certificate and a food item for participating in the tasks. All *substance abuse* participants will receive the same amount of compensation regardless of performance.

Participation

Participation in this research study is voluntary. You have the right to withdraw at any time or refuse to participate entirely without jeopardy to your class status, grade, or relationship with Brigham Young University or the Principal Investigator or with [redacted] Withdrawal from this study will not affect your ability to receive treatment in the Comprehensive Clinics or any other BYU entity or the Utah County Division of Substance Abuse. You are free to choose not to take part in this study and if you do become a participant you are free to stop and withdraw from this study at any time during its course. To withdraw, you can tell a member of the research team at any time that you no longer want to take part. This will discontinue the study procedures.

The researchers may withdraw you from participating in the research if necessary, such as when your reaction to testing is judged to be harmful or if you are not complying with research procedures.

Questions about the Research

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision. You may contact the principal investigator at any time at this address: Jo Ann Petrie, M.S., 1190H SWKT, Brigham Young University, Provo, Utah 84602. Phone: (801) 422-5307, email: joann_petrie@byu.edu. You may also contact Scott Steffensen, Ph.D., at 422-9499 or scott_steffensen@byu.edu.

Questions about your Rights as a Research Participant

If you have concerns about the study or questions about your rights as a research participant you may contact BYU IRB Administrator, A-285 ASB, Brigham Young University, Provo, Utah, 84602;
801-422-1461; irb@byu.edu .

Signatures

I have read this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____

(Please Print)

Signature:_____

Date:_____

_____ _____

Signature of Person Obtaining Consent Date/Time

Visual Color Processing Differences in Males and Females with Substance Abuse and Addiction

Consent to be a Control Drug Free Research Subject

Principal Investigator: Jo Ann Petrie, M.S.
Co-Investigator: Scott C. Steffensen, Ph.D.

Introduction

This research study is being conducted by doctoral candidate Jo Ann Petrie, M.S. and Professor Scott C. Steffensen, Ph.D., at Brigham Young University to better understand sex differences in neural processing during the performance of computer tasks related to visual color processing in those with substance abuse and opiate addiction. You were invited to participate as a *control* in this study because you are a healthy adult who expressed interest in participating in the study. We anticipate that about 60 people will participate in this study.

In order to decide whether or not you wish to be a part of this research study you should know enough about its risks and benefits to make an informed decision. This consent form gives you detailed information about the study, which a member of the research team will discuss with you. This discussion should go over all aspects of this research: its purpose, the procedures that will be performed, any risks of the procedures, and possible benefits. Once you understand the study, you will be asked if you wish to participate; if so, you will be asked to sign this form.

Procedures

You will be designated to either the male or female group for study participation. Both groups will complete the same questionnaires and task procedures, with no differences in task instructions. Participants will receive the same amount of compensation regardless of which study group they are designated to.

For all participants, the study consists of four main parts: 1) filling out an on-line questionnaire and a self –report of any medication/drugs used in past 4 months; 2) give a urine sample for drug analysis; 3) completing a manual color deficiency task and three basic neuropsychological tests, 4) completing computerized tasks while we measure with EEG the small amount of electrical activity that is produced by your body.

- On-line or computer generated questionnaire: Before the physiological measures are obtained, you will be asked to complete a questionnaire on-line including simple questions on your background (for example, your age and marital status);and a section on your medical history and your family's medical history, that is similar to questionnaires you may have filled out at a doctor's office. It should take only 10-15 minutes to complete this questionnaire.
- Medications Used Screening: You will be asked to list all medications that you are currently taking (including insulin, oral contraceptives, prescription medications, over-the-counter

medications, vitamins, diet supplements, herbal supplements, etc.). This will be to determine whether or not your EEG data will be included in the drug-free control database.

- Urine Analysis (UA) Drug Screening Test: You will be asked to give a small urine sample for analysis to verify that your system is truly drug free for control purposes. You will be given a UA test jar that is identified only by the ID number associated with the other tests you are completing today. Before doing those other tests you will be shown to a bathroom next to the EEG lab and given full privacy to complete the test. After following the instructions on the test kit you will place it in a secured box provided which will be collected later by the PI to be taken for analysis. You will then continue with all of the other tests as outlined. In the event that any UA is found positive by the RIA testing done all data associated with that identifying number will be destroyed by the PI and not included in the study. The testing institution will not advise of drugs found, only that the test was positive and will destroy all records once they have advised the PI of all results.
- Color Deficiency test: Administration of the *H.R.R. Pseudoisochromatic Plates* color vision test will take place. You will look at a series of color plates and respond both verbally and with a brush to what you see regarding symbols and shapes on the plates. Completion will take about 5 minutes.
- Neuropsychological tests. We will have you complete 3 standard neuropsychological tests looking for variability in visual, motor and cognitive processing speeds. These will take about 20 minutes.
- Computerized tasks: We will record the activity of your brain while you perform various computerized tasks that involve: 1) presentation of a Stroop effect test including presentations of words and colors in various ways on a computer monitor display requiring you to respond by pressing a keypad as quickly and accurately as possible; 2) responding to flashes of colors presented on the monitor; or 3) watch the monitor as the colors flash with no response. You will also be asked to respond to what numbers you see on the computer screen while wearing 3-D glasses – the same type worn in movie theaters. This is a test of binocular rivalry and you will have a practice session before you start the computer tests. We will measure brain-wave activity from 128 sensors placed on your scalp while you complete the task. The sensors for recording brain wave activity are both painless and harmless; they merely record the small electrical signals produced by your brain. The experimenter will clearly explain where these sensors will be placed before applying them. Completion of these tasks will take about 50 minutes.

Study participation will be completed within one session that will last no longer than 2 hours.

Risks/Discomforts

There are minimal risks for participation in this study. Questionnaires will ask you for information about some sensitive issues, such as your medical history and substance use and any family history of the same. If you are not comfortable answering these questions, you can choose not to answer and discontinue participation in the study. If we should discover, based on the questionnaires, that you experience marked depression or anxiety, we will offer to make an appropriate referral.

Electroencephalogram or EEG is used to measure the electrical ("brain wave") activity of your brain. The risks associated with EEG in this study do not differ from those associated with a standard clinical EEG. The primary risk involves the slight possibility of irritation at the site of sensor application. Every precaution is taken to prevent irritation, and sensors are cleaned and disinfected after each use. We also make an effort to use materials appropriate for sensitive skin.

You will be excluded from study participation if you have a history of *seizures, claustrophobia, fainting, or, brain trauma, or any physiological or psychological disorder, or if you are currently taking any long-term medication or if you have taken prescription pain killers for an extended period of time (6 weeks or more) over the last 4 months*. As mentioned above, the fitting of the electrode net may involve some discomfort to your scalp or even minor pain. You will be carefully monitored throughout the procedures and may stop participating at any time if you become uncomfortable.

Benefits

Please note that the data obtained will not be used for clinical purposes but simply for this research. That is, the data obtained will not be evaluated for the purposes of personal diagnosis or treatment of neurological disease, and this research procedure does not take the place of a clinical EEG procedure.
There are no expected direct benefits to you for participating in this study; however, there exists the possibility of incidental findings of clinical significance from the EEG. Should such findings emerge as a result of your participation we will recommend that you see a physician for an evaluation.

There are no expected direct benefits to subjects for participation in this study. However, it is hoped that through your participation researchers may learn more about gender differences in visual attention and color processing. Furthermore, it is believed that this information can be used in the future to assist researchers to better understand gender differences in identifying and determining treatment outcome measures in substance abuse or addicted patients.

Confidentiality

If you decide to participate in this study, the researcher will get information that identifies you and information about you. This may include information that might directly identify you, such as your name and age. The principal investigator will keep a link that identifies you to your coded information, but this link will be kept secure and available only to the investigator or selected members of the research team. **Any information that can identify you will remain confidential.** The research team will only give this coded information to other members of the research team to carry out this research study. This information will be kept for seven years. After that time it will be destroyed or de-identified, meaning we will replace your identifying information with a code that does not directly identify you.

Any identifiable information that is obtained in connection with this study will remain confidential and will be disclosed only with your permission or as required by U.S. or State law. Data are safeguarded in locked cabinets in locked offices, and electronic data are stored on

password-protected computers. When the results of the research are published or discussed in conferences, no information will be included that would reveal your identity unless your specific consent for this activity is obtained.

Representatives from the BYU Institutional Review Board (the Committee that reviews, approves, and monitors human subject research) may inspect study records during auditing procedures. However, these individuals are required to keep all information confidential.

Compensation

Brigham Young University Students: Brigham Young University students will have the option of participating in the study for extra credit as determined through SONA (e.g., Introductory Psychology class) and a food item for participating in the study or opting for payment. If they opt for payment then they will receive the same payment as non-student control participants. As an alternative to participating in the research for extra credit, BYU students can read an article from a peer-reviewed journal or attend a neuroscience/psychology forum and write a one-to-two page synopsis of the article or forum. All nonstudents and students who elect to participate in the study for payment will be compensated with a $5.00 BYU Bookstore gift card. All *control* participants who desire to receive payment will receive the same amount of compensation regardless of performance.

For those who do not wish to participate in the research, extra credit points can be earned by reading an article from a peer-reviewed journal and writing a one-to-two page paper on the article.

Non-Students: Non-student control drug-free participants receive a $5.00 BYU Bookstore certificate and a pre-packaged food item for participating in the tasks.

Participation

Participation in this research study is voluntary. You have the right to withdraw at any time or refuse to participate entirely without jeopardy to your class status, grade, or relationship with Brigham Young University or the Principal Investigator or with [redacted]. Withdrawal from this study will not affect your ability to receive treatment in the Comprehensive Clinics or any other BYU entity. You are free to choose not to take part in this study and if you do become a participant you are free to stop and withdraw from this study at any time during its course. To withdraw, you can tell a member of the research team at any time that you no longer want to take part. This will discontinue the study procedures.

The researchers may withdraw you from participating in the research if necessary, such as when your reaction to testing is judged to be harmful or if you are not complying with research procedures.

Questions about the Research

We have used some technical terms in this form. Please feel free to ask about anything you don't understand and to consider this research and the consent form carefully – as long as you feel is necessary – before you make a decision. You may contact the principal investigator at any time at this address: Jo Ann Petrie, M.S., 1190H SWKT, Brigham Young University, Provo, Utah 84602. Phone: (801) 422-5307, email: joann_petrie@byu.edu. You may also contact Scott Steffensen, Ph.D., at 422-9499 or scott_steffensen@byu.edu.

Questions about your Rights as a Research Participant

If you have concerns about the study or questions about your rights as a research participant you may contact BYU IRB Administrator, A-285 ASB, Brigham Young University, Provo, Utah, 84602;
801-422-1461; irb@byu.edu .

Signatures

I have read this form and have decided to participate in the project described above. Its general purposes, the particulars of involvement and possible hazards and inconveniences have been explained to my satisfaction. My signature also indicates that I have received a copy of this consent form.

Name of Subject:_____
(Please print)

Signature:_____

Date:_____

_____ _____
Signature of Person Obtaining Consent Date/Time

APPENDIX B3: Demographics Questionnaire

Visual Attention, Color Processing and Physiological Measures

* Required

Pre-Qualification Screening Interview Questions

The purpose of this research is to study female versus male differences in visual color processing through physiological measures, specifically brain activity measured by brain-wave tracings (using electroencephalography or EEG), during performance of computer-presented cognitive tasks.

The following questions will be used to determine if you qualify as a participant for this research.

What is your name? *

What is your gender? *

Female

Male

What is your age? *

Are you color-blind? *

Yes

No

How would you rate your current overall health? *

Excellent

Good

Fair

Poor

Are you currently taking any type of medication, including over-the-counter drugs? *

Yes

No

If so, please list all and for how long. *

Demographic Questionnaire

What is your handedness? *

Right

Left

What is your race?

Are you proficient in English? *

Yes

No

What is your marital status? *

Single

Engaged

Married

Divorced

Widowed

Socio-Economic Background

Education (Please check highest level attained) *

High School

Some Undergraduate

Associate's Degree

Bachelor's Degree
Some Graduate
Master's
Doctorate
Trade School
Annual Household Income: - (use parent's income if still a dependent) *
Under $10,000
$10,001 - $30,000
$30,001 - $60,000
$60,001 - $90,000
$90,001 - $120,000
Over $120,001
Don't know

Medical Questionnaire

General Background
How do you view your present health? *
Excellent
Good
Fair
Poor
If fair or poor, please explain.

Are you currently under the care of a physician? *
Yes
No
If yes, please explain.
Have you consulted or been treated by clinics, physicians, healers or other practitioners within the past year for other than minor illnesses? *
Yes
No
If yes, please explain.
Do you have vision in both eyes? *
Yes
No
Do you wear glasses or contact lenses to correct your vision? *
Yes
No
Have you had Lasik or any other eye surgery? *
Yes
No
Are you color blind? *
Yes

No
Do you have any immediate family members that are color blind? *
Yes
No
If yes, please list. (i.e., mother, father, brother, sister, uncle, aunt grandfather/mother, etc.)
Have you had or do you have any other problems with your eyes or vision? *
Yes
No
If yes, please explain.

Personal Medical History

Have you been hospitalized within the last four months? *
Yes
No
If yes, were you given any painkillers?
Yes
No
Have you ever had any surgeries (in-patient or out-patient) for which you were given a longer than 2-day prescription of opiate pain killers? *
Visual Attention, Color Processing and Physiological Measures Page 5 of 8
Yes
No
If yes, please explain.
Please check if you have had or currently have any of the following conditions: *
Lightheadedness/dizziness
Loss of consciousness/fainting
Seizures or epilepsy
Frequent headaches
Head injury/brain trauma
Abnormal EEG
Memory problems
Numbness or tingling of arms, legs or face
Weakness of an arm, leg, or other body part
Stroke
Paralysis
Decrease in vision
Double vision
Glaucoma
Color blindness
Cataracts
Serious injury to eye
Difficulty sleeping
Psychiatric or psychological disorder
Claustrophobia
Drug or alcohol abuse
Other:
Visual Attention, Color Processing and Physiological Measures Page 6 of 8

Family Medical History

Please check any immediate family members whom you know to have a history of psychiatric or psychological disorders. *
Child
Brother
Sister
Father
Mother
Aunt
Uncle
Grandmother
Grandfather
Please check any members of your family whom you know have a history of drug or alcohol abuse. *
Child
Brother
Sister
Father

Mother
Aunt
Uncle
Grandmother
Grandfather
If there are any other medical histories in your family that you believe we should be aware of, please list below.

ARE YOU WILLING TO HAVE A URINE ANALYSIS TO TEST FOR ANY DRUGS IN YOUR SYSTEM? *
Yes
No

As a participant in this study, additional information will be given to you at the time of your EEG session and you will be asked to sign an "Informed Consent to Be a Research Subject" form.

Do you have any questions at this time? *
Yes
No
If yes, please indicate those concerns. *
Are you willing to participate in this study? *
Yes
No
Submit

APPENDIX B4: Drug Screening Questionnaire

ID #:_____

Date:_____

Drug Screening Questionnaire:

Please list all drugs/medications/prescription/illicit that you have ever taken or are currently taking (including insulin; oral contraceptives; prescription medications – including but not limited to anti-depressants, anti-anxiety, muscle relaxants, sleep aids, narcotic pain-killers, methadone, opiates, etc.; any over-the-counter medications; vitamins; diet supplements; herbal supplements; any Schedule I drugs such as: marijuana; cocaine; heroin; etc.).

Drugs/Medication/etc. being used:	Approximate Date Started or your age when First started:	Date last used:	Dosage:

APPENDIX C

APPENDIX C1: EGI Sensor Net and 10-20 Montage

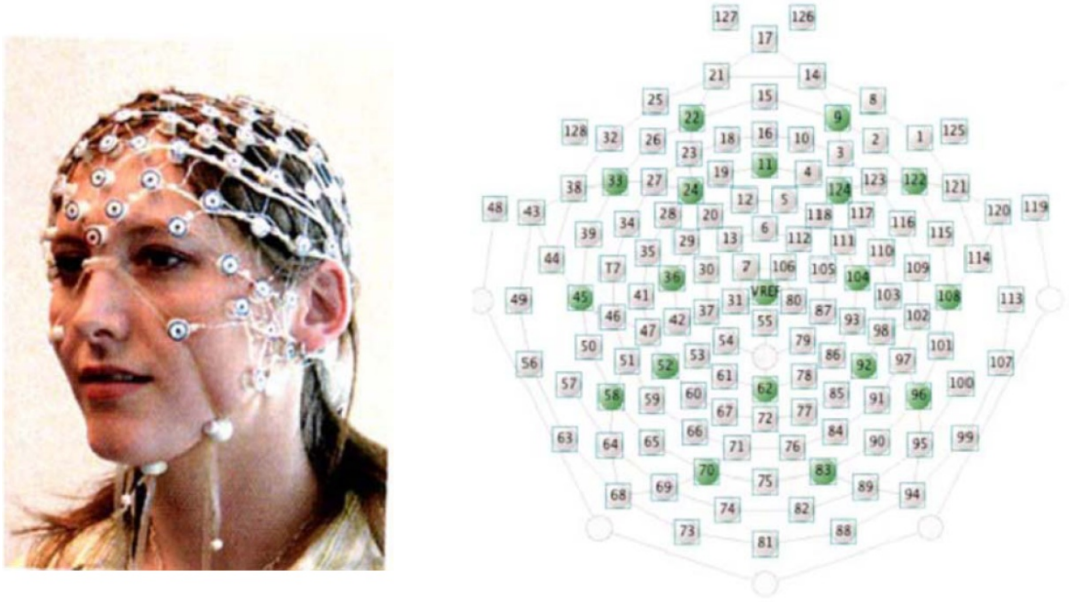
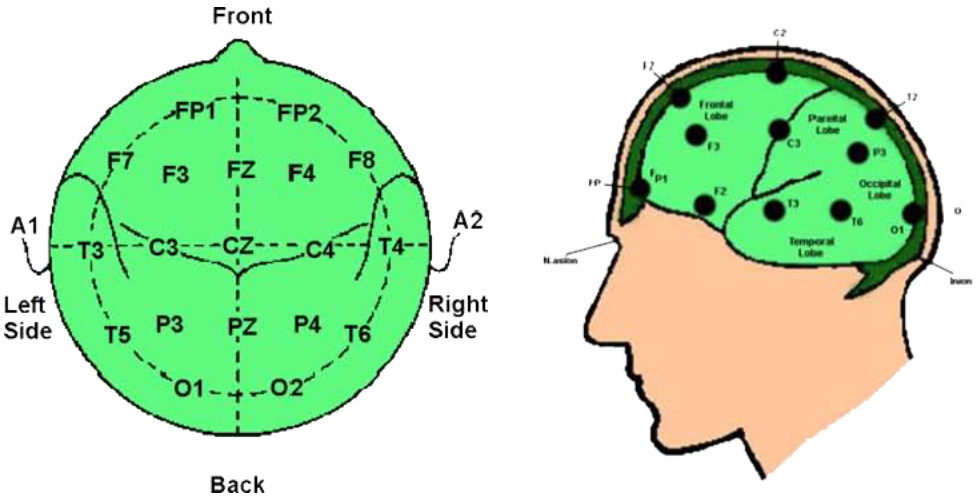


Figure C1. (Left) Well placed sensor net and (Right) EGI System for average mastoid reference in International 10-20 montage.

APPENDIX C2: International 10-20 Map



Note: The International 10-20 System of Electrode Placement is the most widely used method to describe the location of scalp electrodes. The 10-20 system is based on the relationship between the location of an electrode and the underlying area of cerebral cortex. Each site has a letter (to identify the lobe) and a number or another letter to identify the hemisphere location. The letters used are: "F" = Frontal lobe, "T" = Temporal lobe , "C" - Central lobe , "P" = Parietal lobe, "O" = Occipital lobe. (Note: There is no central lobe in the cerebral cortex. "C" is just used for identification purposes only.) Even numbers (2, 4, 6, 8) refer to the right hemisphere and odd numbers (1, 3, 5, 7) refer to the left hemisphere. "Z" refers to an electrode placed on the midline. The smaller the number, the closer the position to the midline. "FP" stands for Front polar. "Nasion" is the point between the forehead and nose. (BrainMaster Technologies, 2012).

Figure C2. The International 10-20 System of Electrode Placement

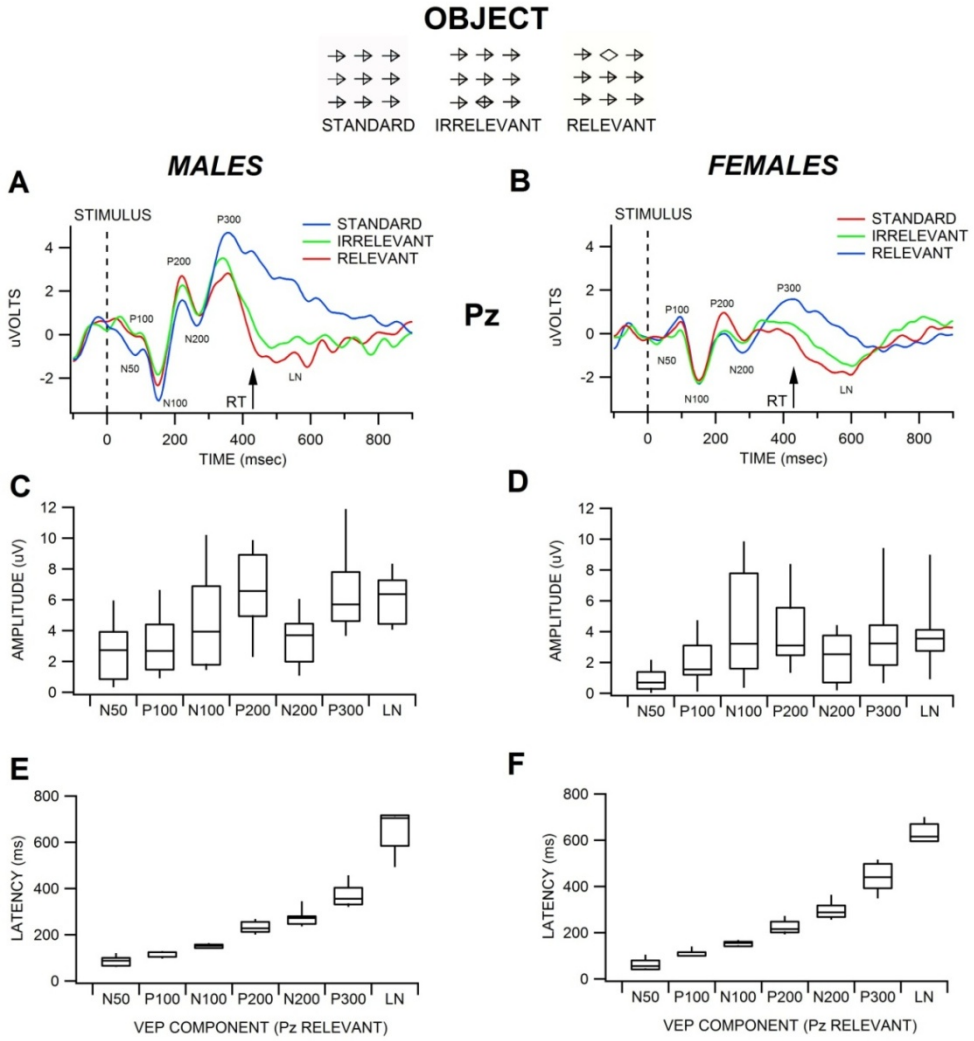
APPENDIX D

EEG Results of Concurrent Object Recognition Task

Gender Differences in Visual-evoked and Event-related Potentials in the Object Recognition Task

In the object recognition task, stimuli (50 msec duration) were randomly presented at 2-4 sec intervals during the 10 min recording session (i.e., Relevant, Irrelevant, and Standard stimuli). One object in the Relevant matrix of right-pointing arrows is a diamond symbol and one object of the Irrelevant matrix is a variation of a diamond and an arrow (see Figure D10 inset). The position of the target symbols was randomly presented in order to avoid errors of gaze. Regardless of matrix, these elements are readily distinguished and "pop-out" from the other eight elements of each matrix. The Standard matrix consists of all right-pointing arrows. Subjects were instructed to press a key pad button when the Relevant stimulus was presented, but to not respond when either the Irrelevant or Standard stimuli were presented. Figure D10A,B compares VEPs elicited by Relevant, Irrelevant, and Standard stimuli superimposed at electrode Pz in males and females in the object recognition task. The parietal and occipital electrode sites evinced the most well-defined combination of early (i.e., task-independent) and late (task-dependent) components of the VEP. The averaged VEP consisted of multiple components which were identified by their respective positions on the waveform, relative to the time of stimulus presentation. Eight distinct alternating positive/negative peaks on the VEP waveform were identified, which occurred at characteristic latencies from the time of stimulus presentation. Early and late peaks of the VEP were identified according to established convention and were labeled N50, P100, N100, P200, N200, and P300, respectively. A late VEP component, termed

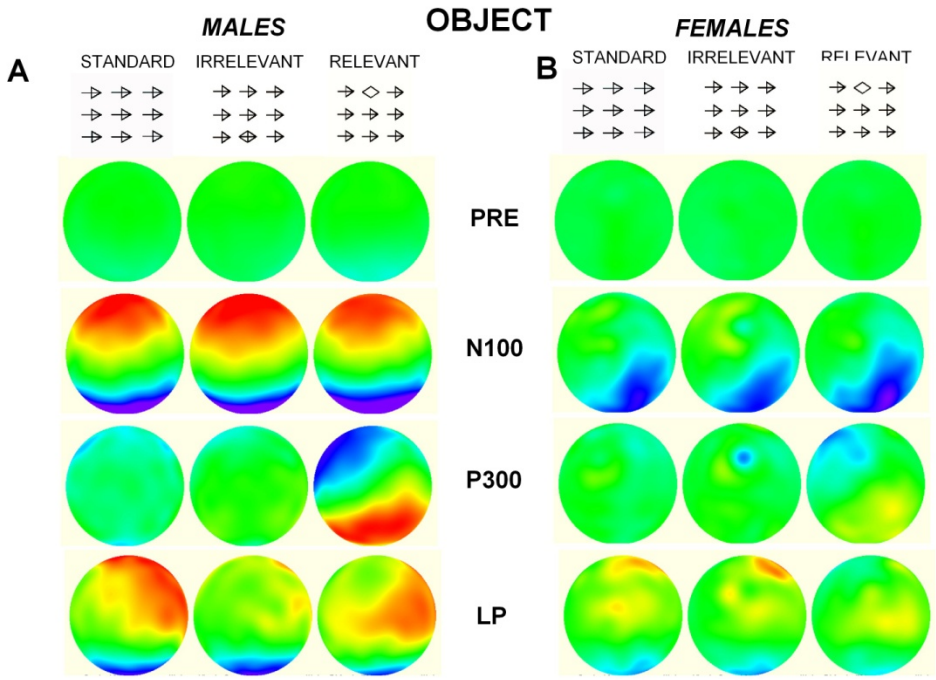
the late negative (LN), was also identified. While the early components (i.e., N50, P100, N100, and P200) of the averaged VEP waveforms were relatively unaffected by type of visual stimulus presented, the late components of the averaged VEP waveforms (N200, P300, and LN) evinced significant amplitude differences across task conditions. These late components are termed event-related potentials (ERPs). For example, the amplitude of the P300 component of the waveform was much greater in amplitude in association with the Relevant stimulus than with Irrelevant and Standard stimuli, in particular at occipital and parietal locations, including Pz shown here. Figure D10C,D compares the distribution of VEP and ERP peak-to-peak N50-LN amplitudes obtained at the Pz electrode site in the object recognition task in males and females (n=10,9, respectively). Figure D10E,F compare the distribution of VEP and ERP N50-LN latencies obtained at the Pz site in males and female (n = 10,9, respectively).



Note: In the object task, insets show the Standard, Irrelevant and Relevant stimuli that were randomly presented at 3-5 sec intervals. Subjects responded to the Relevant stimulus. (A,B) These graphs show grand-averaged VEPs recorded in male and female subjects at electrode Pz in response to Standard, Irrelevant and Relevant stimuli. The vertical scales are normalized to facilitate comparisons between gender. The dashed line indicates the time of presentation of the stimulus. The components of the VEP included the N50, P100, N100, P200, N200, P300, and LN. Reaction time (RT) is shown to the Relevant stimulus. (C,D) Summary of descriptive statistics (i.e., 10-90% range, median, 2nd and 3rd quartiles) of N50-LN VEP amplitudes obtained at Pz for the Relevant stimulus in male and female subjects in the object recognition task. (E,F) Summary of descriptive statistics of N50-LN VEP latencies obtained at Pz for the Relevant stimulus in the object recognition task.

Figure D10. Gender differences in VEP and ERP amplitudes and latencies recorded at electrode site Pz and evoked in the object recognition task.

The EGI 128 electrode system enabled visualization of potentials over the head termed topomaps at a designated window of time before and after the visual stimulus. Figure D11 shows grand-averaged topomaps obtained in male and female subjects before and after the presentation of object stimuli. P300s were localized mostly to the back of the head in male subjects in association with the Relevant stimulus. There was little differentiation of LPs in the object task. Compared to male subjects, P300s and LPs were less prominent (n=24,22, respectively).



Note: In the object task, insets show the object matrices that were randomly presented at 2-4 sec intervals. Subjects responded to the Relevant stimulus. (A) The topomaps (circles) represent grand averaged potentials in male subjects on the head before (PRE), and at 189 msec (N100), 349 msec (P300), and 699 msec (LP) after the presentation of the object stimuli. The color map scales are normalized to facilitate comparisons between gender. The top of each circle is the front of the head and the bottom of each circle represents the back of the head, as if looking down on the head from above. Violet represents extreme negative potentials and red represents extreme positive potentials. The pre-stimulus maps show no recordable activity before the stimulus. Note the differentiation of the P300 associated with Relevant stimulus in males. (B) These topomaps are grand averaged female responses normalized to the color scale for males. Note that females have a less prominent distribution of P300s than males.

Figure D11. Gender differences in the distribution of VEP and ERP mapping in the object recognition task.

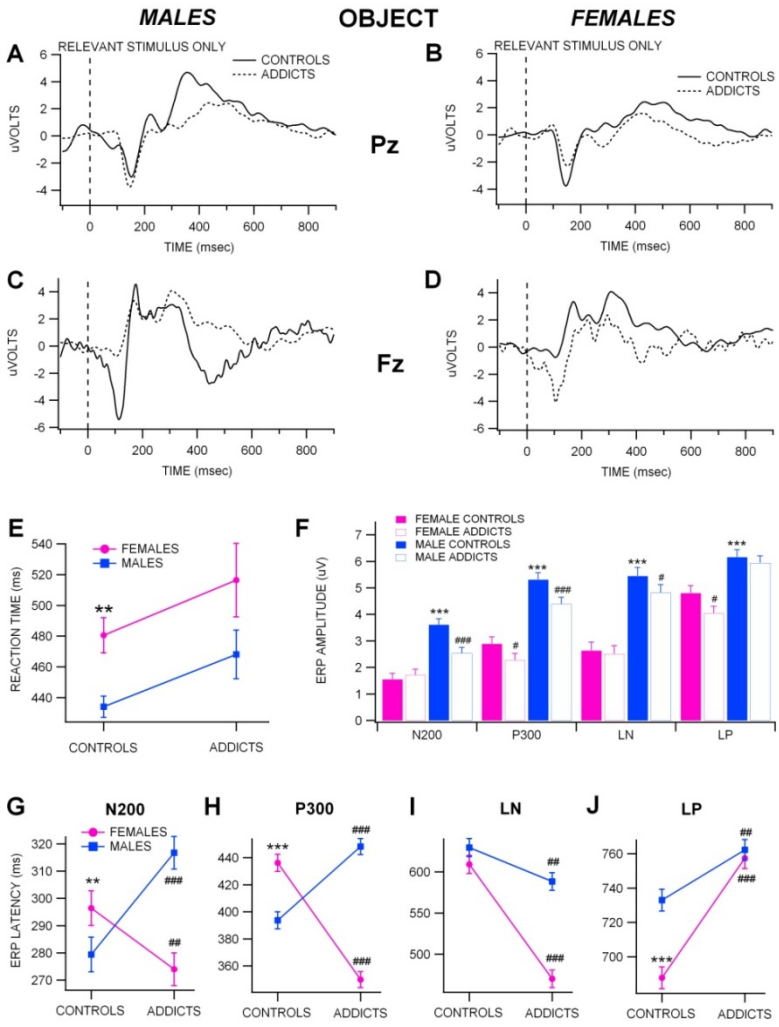
Gender and Addiction Differences in Event-related Potentials in an Object Recognition Task

Based on grand-averaged VEPs, there appeared to be important gender differences in the object recognition (see Figure D10,11). Males were typically characterized by larger P300 and LP ERPs on the waveforms. One of the main objectives of this study was to evaluate cognitive processing in opioid addicts. Thus, we compared ERPs in controls vs addicts in the object recognition task in both males and females (see Figure D12). Figure D12A,B compares grand-averaged VEPs obtained at the Pz site and Figure D12C,D compares VEPs obtained at the Fz site in males and females and controls vs addicts in the object recognition task. Figure D12E compares RTs in males and females and in controls vs addicts. Reaction time was determined from the time of stimulus presentation to the time subjects responded with a key press to the Relevant stimulus. In the object recognition task, females had significantly slower reaction times compared to males ($p = 0.003$, $F_{(1,29)} = 10.3$; n = 17,13). There was no significant difference between male controls and male addicts ($p > 0.05$; n = 17,14) or female controls and female addicts (P>0.05; n=13,13). There was no significant difference between male controls and male addicts (P>0.05; n=17,17) or female controls and female addicts (P >0.05; n=15,18).

While the grand-averaged VEPs and topomaps demonstrated differences between responses obtained with the Relevant stimulus, averaging often underestimates the significance of the effects due to temporal dispersion and other vagaries. Thus, we measured each component of the VEP in each subject and obtained individual measurements. These measurements were then submitted to statistical analysis. The independent variables were gender, 18 electrode locations of the 10-20 System and stimulus condition (e.g., Relevant), while the dependent variables were each of the VEP components. As shown in the methods, to simplify the analysis,

we consolidated the 18 electrodes into front, middle and back of the head. The statistical analysis of amplitude and latency means of individual ERP components at front, middle and back electrodes for males and females. Figure D12F summarizes the gender and addiction effects on ERP (N200-LP) amplitudes in the object recognition task. Given the distribution of potentials associated with the ERP topomaps in the object recognition task (see Figure D11) we chose to evaluate averaged back electrodes of the 10-20 International electrode system (T5, P3, Pz, P4, T6, O1 and O2) for measurements of N200, P300 and LN and averaged front electrodes (FP1, FP2, F7, F3, Fz, F4, and F8) for measurements of LP. For each subject, measurements were extracted at windowed latencies corresponding to each of the ERPs.

Males were characterized by significantly greater N200, P300, LN and LP amplitudes (see Figure D12F). Compared to male controls, opioid addicts were characterized by significantly lower N200, P300 and LN amplitudes (see Figure D12F). Compared to female controls, opioid addicts were characterized by significantly lower N200 and LP amplitudes. Table D1 shows F and P values for each of the ERP amplitudes by contrasts. Latency measurements were also evaluated by gender and by addiction in the object recognition task. Figure d12G-H summarizes the gender and addiction effects on ERP (N200-LP) latencies in the object recognition task. Males were characterized by significantly shorter N200 and P300 latencies and significantly shorter LP latencies compared to females. Compared to male controls, opioid addicts were characterized by significantly slower N200, P300 and LP latencies. Compared to female controls, opioid addicts were characterized by significantly faster N200, P300 and LN latencies and slower LP latencies. Table D2 shows F and P values for each of the ERP latencies by contrasts.



Note: (A,B) These graphs show superimposed grand-averaged VEPs of controls and addicts recorded in male and female subjects at electrode Pz in response to the Relevant stimulus only (i.e., Blue). The vertical scales are normalized to facilitate comparisons between males and females. The dashed line indicates the time of presentation of the stimulus. (C,D) These graphs show superimposed grand-averaged VEPs of controls and addicts recorded in male and female subjects at electrode Fz in response to Relevant stimuli. (E) Summary of reaction time comparisons between males and females and addicts within gender. Females had significantly slower RTs than males in this task. There were no differences between controls and addicts by gender. (F) This graph summarizes ERP measurements in males and females and addicts.
$^{**}p < 0.01$. $^{***}p < 0.001$ between gender, respectively.
$p < 0.01$. ### $p < 0.001$ between controls and addicts.

Figure D12. Gender and Addiction differences in event-related potentials in the object recognition task.

Table D1

Effects of Gender and Addiction on ERP Amplitudes in the Object Recognition Task

ERP	Contrasts	*F* value	*P* value
N200	*Addiction within females*	0.6	0.45
	Addiction within males	22.6	<0.0001*
	Gender	82.6	<0.0001*
P300	*Addiction within females*	5.2	0.02*
	Addiction within males	11.8	0.0007*
	Gender	143.0	<0.0001*
LN	*Addiction within females*	0.2	0.67
	Addiction within males	4.4	0.04*
	Gender	144.2	<0.0001*
LP	*Addiction within females*	4.9	0.03*
	Addiction within males	0.4	0.54
	Gender	46.0	<0.0001*

Note: Degrees of freedom for all values was 228. Asterisks indicate significance.

Table D2

Effects of Gender and Addiction on ERP Latencies in the Object Recognition Task

ERP	Contrasts	*F* value	*P* value
N200	*Addiction within females*	15.1	0.0001*
	Addiction within males	41.7	<0.0001*
	Gender	9.9	<0.002*
P300	*Addiction within females*	97.7	<0.0001*
	Addiction within males	39.0	<0.0001*
	Gender	20.3	<0.0001*
LN	*Addiction within females*	81.7	<0.0001*
	Addiction within males	7.15	0.008*
	Gender	40.8	<0.0001*
LP	*Addiction within females*	67.8	<0.0001*
	Addiction within males	12.0	0.0006*
	Gender	17.4	<0.0001*

Note: Degrees of freedom for all values was 228. Asterisks indicate significance.

APPENDIX E

Neuropsychological Testing Results

Table E1

Neuropsychological Testing Comparisons for Gender and Addiction

	Group Comparisons[¥]				
Tests	Controls M(SD) (n = 31) ± vs Addiction M(SD) (n = 38)	FC M(SD) (n = 16) vs MC M(SD) (n = 15)	FA M(SD) (n = 19) vs MA M(SD) (n = 19)	MC M(SD) (n = 15) vs MA M(SD) (n =19)	FC M(SD) (n = 16) vs FA M(SD) (n = 19)
Finger Tapping	51.3(7.2)	46.9(7.0)	48.2(4.5)	55.9(3.7)	46.9(7.0)
	51.1(7.2)	55.9(3.7)***	54.1(4.9)	54.1(4.9)	48.2(4.5)
Symbol Digit Modalities Test	50.6(8.3)	61.4(10.2)	52.4(7.8)	62.8(12.4)	61.4(10.2)
	62.1(11.1)***	62.8(12.4)	48.8(8.6)	48.8(8.6)***	52.4(7.8)*
Trails A	19.3(5.2) (n = 15)	19.7(4.9) (n = 6)	25.1(5.8) (n = 9)	18.8(6.0) (n = 9)	19.7(4.9) (n = 6)
	26.3(7.1)* (n = 19)	18.8(6.0) (n = 9)	27.3(8.2) (n = 10)	27.3(8.2)* (n = 10)	25.1(5.8)* (n = 9)
Trails B	54.7(23.4) (n = 15)	44.6(10) (n = 7)	73.5 (31.3) (n = 11)	63.5(28.6) (n = 8)	44.6(10) (n = 7)
	72.2(28.8)* (n = 20)	63.5(28.6) (n = 8)	70.6(27.3) (n = 9)	70.6(27.3) (n = 9)	73.5 (31.3)* (n = 11)

Note:; M = mean; SD = standard deviation; FC = female controls; FA = female addicts; MC = male controls; MA = male addicts.

[¥] (Two-tailed *t*- tests).

* p < .05. ** p < .001. *** p < .0001.

± = the n values for the Trails tests are different—we alternated the tests allowing for second testing.