A NEUROBEHAVIORAL INVESTIGATION OF EMOTION PROCESSING AND INTERPERSONAL FUNCTIONING IN ALCOHOLISM

By

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To Lucy (AKA Goose)

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A substantial literature has detailed neurobehavioral compromise in alcoholism. Although classically-defined cognitive processes are predominantly assessed, a growing literature is addressing emotion processing. The study of emotional facial expression (EFE) recognition has gained particular momentum and implicates EFE processing in treatment outcomes. Behavioral investigations conducted to-date suggest an alcohol-related EFE-identification deficit. Research has also begun to elucidate the neural systems/processes underlying compromise. Still, the deficit's precise nature, particularly its valence/emotion specificity, requires clarification. Given the importance of facial expression in non-verbal communication, the relationship between EFE processing and interpersonal problems (IP) also merits further inquiry.

The current study examined neurobehavioral indices of EFE processing and their relationship to IP in alcohol dependent treatment seekers (AD) and healthy controls (CC). Thirty-four ADs and thirty-nine CCs completed an emotion judgement task (EJT), requiring discrimination between happy, angry, and sad EFEs. A sex judgement task (SJT; neutral-expression male/female faces) was administered to strengthen EJT

interpretations. Behavioral (accuracy, reaction time) and neurophysiological (event related potentials; ERP) responses were assessed for both tasks. ERP measures included amplitude and latency of the N170 and later occurring P3. IP was assessed with the Inventory of Interpersonal Problems-64 (IIP-64). EJT, SJT, and IIP-64 measures were analyzed for group differences. EJT and IIP-64 were investigated for within-group correlations.

EJT analyses revealed somewhat less accurate performance and lower P3 amplitudes in ADs than CCs, across all emotions. Although no group-by-emotion interactions emerged, examination of group means suggested a more pronounced difference for anger. IIP-64 analyses indicated greater interpersonal difficulty among ADs. Significant correlations were specific to ADs and anger; poorer accuracy correlated with greater interpersonal difficulty. EJT reaction time, P3 latency, N170 characteristics, and all SJT measures yielded nonsignificant group-related outcomes.

Findings suggest atypical EFE processing in ADs, including subtle behavioral deficiencies and altered neural activity at later processing stages that are specific to the evaluation of emotionally-laden information and generalizable to positive/negative valence. Moreover, alcohol-associated emotion processing difficulties and IP appear to be related. Preliminary data also suggest an enhanced role of anger in this relationship and neurobehavioral compromise. Further investigation is needed to confirm and extend these findings.

CHAPTER 1
INTRODUCTION

Psychoactive substance use and associated disorders have been a significant source of individual and societal burden for centuries. Of the many psychoactive substances with the capacity to alter perceptive, affective, and cognitive processes, alcohol is the most widely used (excluding caffeine; Julien et al., 2010) and continues to pose a significant public health problem in many countries. In the United States, approximately 57% (136.8 million) of Americans age 18 and older are current (i.e. past 30 days) drinkers (Center for Behavioral Health Statistics and Quality (CBHSQ), 2015a). Among this population, an estimated 59.4 million and 16.1 million individuals meet criteria for current binge- (≥5 standard drinks on the same occasion) and heavy- (binge on ≥5 days) alcohol use, respectively (CBHSQ, 2015a).

The misuse of alcohol is associated with a host of physical and mental health problems and remains a prominent source of economic burden, morbidity and mortality. Alcohol misuse is responsible for over 200 billion dollars in annual costs (Sacks et al., 2015) and is currently ranked as the third leading cause of death. Moreover, harmful alcohol use directly accounts for more than 25 chronic diseases and conditions (National Institute on Alcohol Abuse and Alcoholism (NIAAA), 2014), including liver cirrhosis, pancreatitis, and Alcohol Use Disorders (AUDs), the latter of which being entirely alcohol-attributable (World Health Organization (WHO), 2014). Longitudinal data collected via the National Epidemiologic Survey on Alcohol and Related Conditions suggest that approximately 22.7% of alcohol users will become alcohol dependent at some point during their lifetime (Galanter et al., 2014). In the United States alone, an estimated 16.3 million American adults currently suffer from an AUD (Substance Abuse

and Mental Health Services Administration (SAMHSA), 2014). Accordingly, alcohol accounts for the majority of substance use disorders (CBHSQ, 2015b) and is the leading reason for receipt of substance use treatment (SAMHSA, 2013).

Alcohol Use Disorders Defined

AUDs are characterized by a well-defined set of criteria that have been established and periodically revised by the medical and scientific community. Among the various diagnostic tools available, two conventional sets of criteria are most commonly used to diagnose AUDs: 1) the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM) and 2) the World Health Organization's International Classification of Diseases (ICD). Although some variability in terminology and criteria exists between these diagnostic tools and within their respective versions (e.g., Alcohol Dependence in DSM-IV and ICD-10 vs. moderate / severe Alcohol Use Disorder in DSM-5), broad similarities permit a common framework. Recent versions of the DSM (DSM-IV (1994) and DSM-5 (2013)) and ICD (ICD-10 (1993)) are homogeneously comprised of AUD criteria that address: 1) tolerance (requiring a greater amount of alcohol to achieve the same effect), 2) withdrawal (e.g., nausea, tremors, or sweating in the absence of alcohol), 3) impaired control of drinking behaviors, 4) neglect of important activities, 5) excess time dedicated to alcohol-related activities, and 6) continued use despite physiological and psychological consequences (Hasin, 2003; NIAAA, 2016; American Psychological Association, 2014). Therefore, AUD can be broadly characterized as regular and excessive alcohol consumption despite negative consequences, a loss of control over drinking behaviors, and the likely presence of physiological symptoms. Although the ICD has both clinical and scientific utility, the majority of the scientific literature relevant to the current investigation, and

subsequently cited below, concerns Alcohol Dependent populations per DSM-IV criteria. Given that variance between and within these diagnostic tools is not a primary focus of the current report, diagnoses determined via all of these tools are generally referred to as ‘Alcohol Use Disorders’ and ‘alcoholism’ (individuals referred to as ‘alcoholics’) throughout the Introduction and Discussion for ease of communication. Given the nature of the available literature, these terms will principally denote alcohol dependence. Unless otherwise stated, all alcoholic participants in the studies noted hereafter have completed detoxification and are typically in or beyond their third week of sobriety.

Neurobehavioral Correlates of Alcohol Use Disorders

Prevention and successful treatment of AUDs partially relies on the thorough characterization of predictors, correlates, and consequences of harmful alcohol-use behaviors. Given the prevalence of and individual/societal burden caused by AUDs, it is no surprise that substantial resources have been dedicated to better understand them. The deleterious effects of chronic heavy alcohol use have been widely investigated over the last several decades, offering significant insight to the neurobehavioral correlates of alcoholism. Studies have revealed a host of alcohol-related structural (Fein et al., 2002; Makris et al., 2008), functional (Hermann et al., 2007; Jung et al., 2014; Pfefferbaum et al., 2001), and cognitive abnormalities (Sullivan et al., 2000; Chanraud et al., 2007).

Detoxified alcoholics frequently show reductions in white (Agartz et al., 2003a; Demirakca et al., 2011; Pfefferbaum et al., 2006) and grey matter (Agartz et al., 2003a; Demirakca et al., 2011; Chanraud et al., 2009), enlarged ventricles, and widened sulci (Mann et al., 2005; Wobrock et al., 2009; see Oscar-Berman et al., 2014 for a recent review). This neurostructural atrophy has been observed in both whole-brain and region-specific manners, with the frontal lobes, limbic structures (e.g., amygdala,

cingulate cortex, hippocampus, and temporal lobe gyri), cerebellum, and their respective connections showing particular vulnerability to alcohol's deleterious effects (Bates et al., 2013). Furthermore, studies implementing functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and electroencephalography (EEG) provide evidence of atypical cerebral blood flow (e.g., Bagga et al., 2014; Müller-Oehring et al., 2013), brain metabolism (e.g., Dao-Castellana et al., 1998), and neurophysiology (e.g., Namkoong et al., 2004; Roopesh et al., 2010), respectively (Oscar-Berman et al., 2014). At the behavioral level, domain-specific compromise after chronic heavy alcohol consumption has been extensively detailed for a variety of classically-defined cognitive abilities.

Although not all alcoholics exhibit cognitive insult during abstinence (i.e. a period in which alcohol is not consumed), mild to severe impairment can be observed in approximately 30%-80% of this population after detoxification (Bates et al., 2002a). Alcohol-related deficits span a broad range of cognitive functions. Whereas automatic and overlearned processes (e.g., crystalized intelligence) are typically spared, notable impairments are observed for more complex and effortful processes (Nixon & Glenn, 1995; Stavro et al., 2013). More specifically, an extensive literature has documented deficient visuospatial, planning, and problem solving skills within the domain of fluid ability, as well as impaired prospective memory, episodic memory, and novel learning skills within the domain of learning / memory (Bates et al., 2013; Pitel et al., 2014). Moreover, executive functions such as response inhibition, mental flexibility, self-monitoring, and working memory are suggested to be particularly vulnerable to alcohol-related compromise. Other cognitive functions commonly affected in populations with

AUD include psychomotor skills, information processing speed, and attention (Bates et al., 2013; Pitel et al., 2014). Many of these impairments persist throughout prolonged abstinence (Fein et al., 1990; Stavro et al., 2013); however, partial recovery of cognitive function (Fein et al., 2006) and brain atrophy (Agartz et al., 2003b; Demirakca et al., 2011; Gazdzinski et al., 2010) is reported (Oscar-Berman et al., 2014).

In an effort to explain alcohol-related cognitive insult, several theories of alcohol's effects on neural structure and function have been proposed. Among these theories, the frontal lobe hypothesis suggests that anterior neural structures are most susceptible to alcohol's deleterious effects. This hypothesis arose from an accumulation of studies showing diminished neurobehavioral functioning among alcoholics in domains thought to be subserved by frontal structures (e.g., executive functions; Parsons, 1987; Parsons & Leber, 1982). However, the frontal lobe hypothesis does not fully account for the heterogeneity or lack of frontal lobe dysfunction seen in some alcohol-related investigations and fails to explain commonly observed deficits in other neural regions and their associated functions. Alternatively, the lateralization hypothesis proposes that right hemisphere structures/functions are disproportionately vulnerable. Support for this hypothesis stems from reports of deficient right-hemisphere lateralized non-verbal functions in alcoholics, with left-hemisphere lateralized verbal abilities left relatively intact (Parsons, 1987; Parsons & Leber, 1982). Despite support for the lateralization hypothesis, this pattern of impairment is not always observed (Stavro et al., 2013). A third theory suggests that alcoholism affects the brain in a global manner, inducing mild disruptions to multiple brain areas that variably contribute to functional neural systems (Parsons & Leber, 1982). This view, termed the 'generalized diffuse' hypothesis, has

garnered considerable support over the years (e.g., Beatty et al., 2000; Stavro et al., 2013; Tivis et al., 1995). Consequently, an attempt to identify focal lesions in alcoholics has been largely abandoned. This shift in research has led to the widespread investigation of alcohol-related processing deficits, which has, in turn, suggested that cognitive impairment may be the result of inefficient processing (Nixon & Bowlby, 1996) and limited cognitive resources (Fama et al., 2004; Smith & Oscar-Berman, 1992).

Characterization of AUDs and the neurobehavioral systems they affect has considerable potential to inform effective treatment and patient recovery. Despite a rich history of research concerning the neurobehavioral correlates of alcoholism, systematic investigation has been somewhat limited to classically-defined cognitive processes. Among the functional domains that have received relatively less attention and merit additional investigation, emotion processing has significant potential to contribute to a more comprehensive understanding of AUDs.

Emotion Processing and Alcohol Use Disorders

The perception, interpretation, and regulation of emotional states are essential survival mechanisms that influence cognitive processes (e.g., decision making) and subsequent behaviors (Adolphs, 2002; Damasio, 1999). Among their many functional roles, these affect-related components, or emotional processes, serve as key facilitators of social communication. More specifically, effective processing of internal and external (auditory and visual) emotional cues promotes socially-acceptable and situation-appropriate interpersonal interactions (Adolphs, 2002; Damasio, 1999).

The study of emotion processing in populations with AUD suggests dysfunction in a variety of affect-related areas. For example, alcoholics commonly exhibit alexithymia, a condition characterized by the reduced ability to experience, identify, and

describe personal emotional states (Kopera et al., 2014). Blunted affect, disinhibition, altered reward processing, antisocial personality traits, and difficulty interpreting the verbal and non-verbal affective cues of others have also been noted (Oscar-Berman & Marinković, 2007; Parsons et al., 1987). Altered emotional functioning is thought to play a primary role in AUD development and disease progression (Clark et al., 2007; Zywiak et al., 2003). Relatedly, emotion processing deficits can negatively impact psychosocial and interpersonal domains of daily living, for which problems are commonly reported in alcoholics and serve as important determinants of recovery (Marlatt, 1996).

One component of emotion processing that plays a key role in interpersonal functioning and has received increased attention in AUD-focused research over the last decade is emotional facial expression (EFE) identification (Uekermann & Daum, 2008). A growing body of literature suggests that alcoholism is associated with a decreased ability to accurately identify and interpret the EFEs of others. Facial expression is a particularly important component of non-verbal communication of affective states (Eimer & Holmes, 2002). Although some controversy exists as to which facial expressions are categorically defined as emotions, the scientific community has largely agreed that faces code for six basic emotions: happiness, anger, sadness, fear, surprise, and disgust (Uekermann & Daum, 2008).

Altered processing of emotional facial cues can lead to misinterpretation of others' thoughts, feelings, and intentions which might, in turn, yield negative social outcomes. For example, misperception of anger might result in altercation and interpersonal conflict. Furthermore, impaired emotion processing and resultant interpersonal difficulties may promote avoidance of social situations. Importantly, social

isolation has the potential to hinder treatment efforts and increase risk of relapse in recovering alcoholics (Uekermann & Daum, 2008). In fact, poorer EFE identification has exhibited a direct relationship with increased likelihood of treatment drop-out (Foisy et al., 2007a) and a greater number of medical detoxifications (Townshend & Duka, 2003). Clearly, the investigation of emotion processing in alcoholism has important and clinically-relevant implications. Characterizing the nature and extent of alcohol-related EFE processing deficits, and the way they relate to interpersonal difficulties, might better inform treatment efforts and ultimately facilitate AUD recovery.

The study of EFE processing among abstinent alcoholics gained momentum in the early 2000's. Much of this research has been conducted in Belgium by a single group of investigators and has largely concerned behaviorally circumscribed markers of EFE processing. These studies, along with the few originating from other countries (e.g., England, Germany, Italy, United States), most commonly assessed behavioral outcomes by measuring accuracy of EFE identification and/or perception of emotional intensity depicted in facial expressions of emotion (i.e. intensity ratings; Bora & Zorlu, 2017). Reaction time has been investigated to a lesser extent, as many behavioral studies have either elected not to restrict stimulus-presentation and response windows or to omit reaction time findings when response windows have upper limits. Some of these investigations have used EFE identification tasks that consist of face stimuli expressing full-scale emotion (i.e. maximum (100%) intensity). Others utilize faces that are more likely to be encountered in real-world situations and, therefore, have greater ecological validity (Kornreich et al., 2003). In these cases, faces either depict 1) a lesser degree/intensity of emotion (i.e. EFE morphed with neutral facial expression to depict a

proportion of the intended emotion; e.g., 30% happy / 70% neutral) or 2) mixed emotions (i.e. two different EFEs morphed with one another, resulting in one face that expresses a proportion of each emotion; e.g., 30% happy / 70% fear).

Previous behavioral investigations of alcoholics, relative to control samples, have revealed less accurate EFE identification for maximum intensity expressions (Quaglino et al., 2015; Carmona-Perera et al., 2014; Kornreich et al., 2013; Maurage et al., 2008a; Frigerio et al., 2002), emotion/neutral morphed expressions (Philippot et al., 1999; Kornreich et al., 2003; Kornreich et al., 2001a; Foisy et al., 2007a; Kornreich et al., 2001b), and mixed emotion expressions (Acharya & Dolan, 2012; Townshend & Duka, 2003; Maurage et al., 2007a). Findings also suggest that alcoholics have a tendency to overestimate emotional intensity in facial expressions (Townshend & Duka, 2003; Philippot et al., 1999; Kornreich et al., 2001a; Maurage et al., 2009; Kornreich et al., 2013; Kornreich et al., 2001b; Foisy et al., 2007a) and might require greater intensity of emotional expression for accurate EFE identification (Frigerio et al., 2002). Although response latency is less frequently explored, alcohol-related reaction time delays in EFE identification have been previously noted in a handful of reports (e.g., Maurage et al., 2007a). While general psychomotor slowing is occasionally observed in abstinent alcoholics regardless of neurobehavioral demands, some studies have shown emotion specific reaction time delays, without generalizability to the identification of other facial attributes (e.g., sex, race, age; Maurage et al., 2008a; Foisy et al., 2007b). Importantly, other investigations provide evidence that alcohol-related impairments in EFE identification are not due to a reduced ability to label emotions (i.e. semantic deficit), but

rather, appear to be attributable to deficient perceptual and/or top-down integrative processes (Kornreich et al., 2016).

Despite substantial evidence for an emotion processing impairment, behavioral deficits in EFE identification are not always observed among alcoholics (see Uekermann et al., 2005 for null findings). Moreover, when impaired performance is noted, the precise nature of this deficit has yielded equivocal findings. The greatest inconsistencies are observed for valence-specific outcomes. Some investigations suggest that heavy chronic alcohol consumption might induce EFE processing deficits specific to negatively valenced emotions (i.e., unpleasant; e.g., sad), with positively-valenced emotion (i.e. pleasant; e.g., happy) identification spared. More specifically, these studies reveal less accurate identification of negative valence among recently abstinent alcoholics, including, but not limited to, anger and/or sadness, and a preserved ability to identify happiness (Quaglino et al., 2015; Acharya & Dolan, 2012; Carmona-Perera et al., 2014; Frigerio et al., 2002; Townshend & Duka, 2003; Kornreich et al., 2013) and/or surprise (Acharya & Dolan, 2012; Carmona-Perera et al., 2014; Townshend & Duka, 2003). Investigations that demonstrate alcohol-related overestimation of the emotional intensity depicted in EFEs have also suggested negative-valence specificity. In other words, alcoholics might overestimate the amount of negative, rather than positive, valance expressed in all EFEs (positively and negatively valenced expressions; Foisy et al., 2007a), with some studies showing the particular overestimation of anger (Frigerio et al., 2002; Townshend & Duka, 2003; Philippot et al., 1999; Maurage et al., 2009).

Despite evidence for a valence-dependent deficit, a number of other investigations have observed impaired EFE identification for both positively and negatively valenced stimuli (Maurage et al., 2008a; Philippot et al., 1999; Kornreich et al., 2001a; Kornreich et al., 2003; Maurage et al., 2007a; Kornreich et al., 2001b). Importantly, when impaired EFE identification of positive-valence has been reported, it has been consistently accompanied by an additional deficit for at least one negatively valenced emotion. Therefore, EFE processing impairments might be more pronounced for negatively valenced emotions.

Although scientific evidence generally supports a behavioral deficit for negatively valenced EFEs, inconsistencies have prevented conclusions regarding the deficit's specificity to emotions within this valence category. For example, investigation of recently abstinent alcoholics, as compared to community controls, has revealed less accurate identification of anger, but preserved recognition of fear (Kornreich et al., 2001a). Some studies have shown support for this finding and reveal additional impairments for the identification of sad and disgusted EFEs (Acharya & Dolan, 2012; Philippot et al., 1999; Kornreich et al., 2001b). However, several reports note contradictory results. Alcoholics have alternatively exhibited a preserved ability to identify anger and sadness but less accurate identification of fear. This alcohol-related deficit for fear has been observed in both the presence (Carmona-Perera et al., 2014) and absence (Townshend and Duka, 2003) of impaired disgust recognition. Other reports have noted unimpaired fear recognition along with typical anger and sadness identification, and otherwise suggest a deficit specific to disgust (Quaglino et al., 2015). The preserved identification of anger and sadness observed in these studies has been

reported by another team of researchers (Kornreich et al., 2013). Yet, in contrast to these findings and those noted above, alcoholics have also exhibited less accurate identification of sadness with unimpaired recognition of anger (Frigerio et al., 2002).

In an attempt to clarify inconsistent findings, a recent meta-analysis (Bora & Zorlu, 2017) estimated mean effect sizes across studies of facial emotion recognition impairments in abstinent alcoholics. The largest effect sizes were observed for anger and disgust, suggesting that the alcohol-related EFE identification deficit might be most pronounced for these emotions. However, this meta-analysis only included 12 studies of EFE processing (analyses were limited to behavioral studies of four or more maximum intensity or emotion/neutral-morphed expressions that reported sufficient information for calculation of effect sizes and standard errors), reinforcing the need for further investigation. Taken together, these highly variable outcomes currently preclude conclusions regarding an emotion-specific deficit for negatively valenced EFEs.

Contributing to this confusion, some investigations have revealed global, rather than valence- or emotion- specific, EFE identification impairments. In these studies, abstinent alcoholics show poor identification across all emotions of interest. Global deficits have been noted with simple two-choice paradigms using happy, angry, and sad EFEs (Maurage et al., 2008b), as well as with more complex response demands and additional EFE stimuli (e.g., evaluation of 4 EFE stimuli and response options for 8 emotion expressions; Kornreich et al., 2003). Clearly, behavioral deficits in the context of emotion-/valence- specific findings require further investigation to elucidate the precise nature of AUD-related impairment. Assessment of EFE processing at the neural level might provide additional insight and help to clarify inconsistent findings.

Behavioral tests provide gross measures of function, which offer insight to the external manifestations of complex neural processes. Subtle deficits and the use of alternate strategies might not be detected by these assessments when administered in a laboratory setting. Furthermore, the neural structures and specific processes implicated in typical and atypical EFE identification cannot be fully delineated with behavioral measures. Therefore, examining the neural correlates of EFE processing impairments may provide a more complete understanding of dysfunction in AUDs.

To date, the characterization of alcohol-related EFE processing deficits at the neural level remains relatively understudied (D'Hondt et al., 2014). Among existing reports, fMRI investigations have suggested altered activation using a variety of EFE-based tasks. Although behavioral impairment is not always observed with these assessments (potentially due to relatively low task complexity; Charlet et al., 2014; Salloum et al., 2007), atypical neural activation is consistently reported. Relative to non-alcoholic controls, abstinent alcoholics have exhibited reduced neural activation while performing tasks that assess emotion recognition (O'Daly et al., 2012), intensity evaluation (Salloum et al., 2007), valence (positive vs. negative) categorization (Maurage et al., 2013), and implicit emotion processing (Marinkovic et al., 2009; Charlet et al., 2014).

Brain regions showing deficient activation in response to the EFE evaluation include the anterior cingulate cortex (Salloum et al., 2007), orbitofrontal cortex, insula (O'Daly et al., 2012), right middle frontal gyrus (Maurage et al., 2013), amygdala, and hippocampus (Marinkovic et al., 2009). Compensatory neural activity has also been suggested, in the absence of significant neural or behavioral deficits, for regions

associated with higher-order functions (e.g., prefrontal cortex; Charlet et al., 2014). Despite between-study variability in methodology and region-specific findings, many of these structures have been broadly implicated in EFE processing among healthy non-alcoholic populations (Adolphs, 2002). For example, studies that utilize imaging techniques, single-cell recordings, and focal-brain-lesioned populations have shown that the evaluation of facial features and expressions involves the orbitofrontal cortex, amygdala, anterior cingulate cortex, parietal cortex, inferior parietal cortex, occipito- and infero- temporal cortex, as well as other frontal structures (Adolphs et al., 1996; Blair et al., 1999; Fried et al., 1997).

Clearly, EFE identification recruits a host of brain regions. These regions contribute to several component processes of EFE analysis and do so in a temporally dynamic fashion. Although impractical to assign a discrete neural structure to a single component process (Adolphs, 2002), neural network theories of EFE processing suggest temporally-dependent structural contributions. Evidence-based theories propose that EFE processing begins with structural encoding of facial features for the formation of crude stimulus representations and categorizations (e.g., face vs. other-object). This rapid and early perceptual processing typically occurs within approximately 100 ms from stimulus onset. It is suggested to involve brain regions comprising the core visual system, including early visual cortices (e.g., V1 and V2) and subcortical structures such as the superior colliculus and pulvinar thalamus. More anterior regions (including visual association cortices) are thought to be subsequently recruited for further perceptual processing. By approximately 170 ms, information processing via posterior temporal cortices and the fusiform gyrus purportedly allow for the formation of

detailed structural representations. Representations of animated (e.g., expression) and static (e.g., identity) facial features, respectively contained in the superior temporal sulcus and lateral fusiform gyrus, are collectively provided to higher-order cognitive systems. During the later stages of EFE processing (~300 ms post stimulus onset), the anterior cingulate cortex, prefrontal cortex, and somatosensory regions are allegedly recruited by this dynamic network for the formation of conscious EFE stimulus representations, control of thoughts and behaviors, and elicitation of accompanying internal states (e.g., associated feelings). Parallel neural activation of the amygdala, orbitofrontal cortex, and ventral striatum is likely to modulate early and late EFE processing stages. Neuronal projections to and from these structures can influence attentional allocation for facial features, refine stimulus representations and classification according to their emotional significance, modulate retrieval of stored emotion-related knowledge, and induce an emotional response (for a review of these concepts, see: Adolphs, 2002; Eimer & Holmes, 2007).

In sum, neural network theories propose that EFE processing involves the fluid and collective effort of several brain regions that have variable and shared contributions to temporally-defined component processes. One way to measure the collective contributions of this complex neural network is through the use of techniques with superior temporal resolution. Electrophysiological techniques are particularly well suited for the investigation of discrete, temporally-defined neural processes that arise from the summated activity of neural systems and constitute global behaviors.

Electroencephalography (EEG) allows for the recording of synchronous post-synaptic electrical brain activity at the level of the scalp. Event-related potentials (ERPs)

can be extracted and averaged from continuous EEG recordings to reveal voltage oscillations, time-locked to specific internal and external events (Luck et al., 2014). ERP waveforms are thought to reflect certain psychological processes and are typically measured with amplitude and latency (Porjesz & Begleiter, 1995; See Coles et al., 1991 for a more thorough review on ERPs). ERP components are typically named according to the direction of their deflection (i.e. P for positive and N for negative) and the approximate time at which they peak from stimulus onset (e.g., P100 is a positive-going waveform, peaking approximately 100 ms after stimulus onset).

Researchers have largely relied on neurophysiological measures to better characterize the component processes of a given function. Whereas behavioral testing provides gross measures of cognitive function, neurophysiology allows for the observation of neural activity on a millisecond time course. Thus, individual components, associated with specific psychological/cognitive processes, can be separated from global behaviors and assessed as distinct stages (Tipper, 2004). ERP components can be broadly categorized into two general stages: 1) early exogenous processes that are stimulus-driven and largely automatic (early latency; e.g., 50-100 ms) and 2) later endogenous processes that are associated with higher order functions, such as conscious appraisal, the formation of complete stimulus representations, and decisional processes (mid- and late- latency; e.g., 300-500 ms; Fein et al., 2010; Luck, 2014). Evidence suggests that both earlier and later ERP components, reflecting various processing stages, can be influenced by emotional information portrayed in a stimulus. Mid-latency components have exhibited sensitivity for detecting emotional versus neutral facial expressions, whereas later-latency components have shown

decipherable activation between EFEs (e.g., happy vs. fearful; For a review, see Hajcak et al., 2012). ERP aberrations suggest atypical activation of neural networks that contribute to a given process. Similar to neuroimaging, atypical ERP measures may be observed in the absence of behavioral impairment, thus, providing a more sensitive index of alcohol-related functional abnormalities.

To date, relatively few ERP investigations of EFE processing have been conducted in the AUD population. Among them, significant variability exists in the tasks used. Given that ERP elicitation and interpretation are highly task dependent, components of interest have also differed. Nonetheless, ERP investigations have begun to shed light on the neural correlates that underlie EFE-related behavioral impairments in recently abstinent alcoholics. The currently available literature includes ERP studies of both implicit and explicit emotion processing.

Implicit EFE processing has been previously examined with emotional oddball paradigms. Although task demands do not call for explicit evaluation of emotional expression, they require the processing of stimuli that contain emotional information (O'Daly et al., 2012). Oddball tasks are simple and widely implemented paradigms used in the broader ERP literature to investigate attention-mediated processing. In an oddball task, rare target stimuli are presented within a series of frequent (i.e. standard) non-targets (Luck et al., 2014). For the emotion variation of this task, simple stimuli (e.g., objects and shapes) typically used in a classical paradigm are substituted with stimuli that contain emotional content, such as EFEs. Two investigations have used the emotional oddball task to assess earlier and later stages of EFE processing among recently-abstinent alcoholics. These studies reveal behavioral impairment, as well as

electrophysiological markers of deficient implicit emotion processing among individuals with AUD, relative to healthy community controls. However, the specific processing stages implicated in behavioral impairment differ between studies.

Concerning earlier processing stages, both investigations assessed the N170 in response to facial expression stimuli. The N170 is an ERP component that shows preferential activation for human faces and is thought to reflect higher-level perceptual processing stages, such as stimulus encoding, which allows for the formation of complete stimulus representations (Bentin et al., 1996; Rossion & Jacques, 2011). One study demonstrated emotion- and valence- specific alterations of the N170 among recently abstinent alcoholics, compared to healthy control participants. More specifically, alcohol-related N170 latency delays were more pronounced for sad and fearful EFEs than neutral and happy expressions presented at varying emotional intensities (Maurage et al., 2007b). In contrast, the same group of researchers observed typical N170 component characteristics among a different group of alcoholics when mixed emotion expressions of anger and disgust were presented under varying oddball-task conditions (Maurage et al., 2008c).

Both of these studies also examined the later occurring P300 (i.e. P3) component, which is generally associated with decisional processing prior to initiation of a motor response (e.g., button press; Hansenne, 2006; Polich, 2004) and is thought to reflect the amount of information extracted from a given stimulus (Donchin et al., 1986; Campanella et al., 2010; Campanella et al., 2009). Altered P3 activation was unanimously reported across investigations. However, Maurage and colleagues observed delayed latency and attenuated amplitude of the P3 across all facial

expressions (neutral and emotional) in their earlier investigation (Maurage et al., 2007b), whereas their later report suggested an anger-specific processing deficit among alcoholics (Maurage et al., 2008c). Regarding the latter finding, healthy controls showed neural activation suggestive of enhanced processing of, and greater difficulty disengaging neural resources from, anger, and alcoholics failed to show this beneficial adaptive response (assuming anger is a biologically relevant cue for danger and altercation). Atypical component characteristics were accompanied by delayed reaction times in both investigations, with alcoholics showing delays that were either specific to sad EFEs (Maurage et al., 2007b), or generalized to all EFEs (Maurage et al., 2008c).

Taken together, it is not entirely clear if the implicit emotion processing deficit presents for alcoholism at higher level perceptual processing stages (i.e. N170). However, investigation of P3 component activation seems to consistently reveal atypical characteristics among alcoholics suggesting altered neural activation, at least at decisional processing stages, that manifests as behavioral impairment. Still, conflicting findings and varying task demands preclude strong conclusions regarding emotion and valence specificity.

Although the oddball task is a popular and useful paradigm for electrophysiological research, relatively low task complexity often yields ceiling effects for behavioral measures of accuracy. Furthermore, task demands do not necessarily elicit explicit emotion processing, for which identification and categorization of emotions is necessary. A handful of investigations have assessed explicit emotion processing, in which tasks demanded discrimination between two or three EFEs. In other words,

participants were required to identify which of two (or three) emotions was expressed by a given face stimulus.

Given that a markedly limited number of ERP studies have assessed explicit EFE processing in recently abstinent alcoholics, methodology, EFE stimuli, components of interest, and study outcomes are highly variable between them. One of these investigations (Maurage et al., 2008b) examined emotion processing in alcoholics using an emotion judgement task that required the discrimination of happy, angry, and sad EFEs, morphed with neutral expressions to depict varying degrees of each expression (35%, 65%, 95%). Relative to healthy community controls, abstinent alcoholics exhibited delayed reaction times and atypical ERP component characteristics across all emotions. P100, N170, and P3 latency delays, as well as attenuated P3 amplitude were noted. The administration of control tasks, including a sex judgement task and a simple reaction time task, further revealed that atypical P3 elicitation and reaction time delays were specific to emotion judgement. Taken together, these findings might suggest an EFE processing deficit that is valence general, attributable to deficient processing at later decisional stages, and specific to the evaluation of emotionally-laden information. Although this study holds significant merit, interpretation of alcohol-related findings in this report are somewhat obscured by the additional assessment of comorbid depression, which was the primary focus of investigation.

A different pattern of results was observed by the same investigative team in an assessment of unimodal versus multimodal (visual and auditory emotional cues) emotion processing. In unimodal visual conditions, Maurage and colleagues (2008d) used maximum intensity happy and angry faces to investigate EFE identification.

Comparison of recently abstinent alcoholics and healthy controls revealed alcohol-related performance deficits across all emotional expressions. Although their emphasis on multimodal investigation makes it somewhat difficult to delineate findings explicitly pertaining to emotion processing in the visual modality, the report clearly communicates P3 amplitude attenuation among alcoholics that is specific to angry EFEs and the absence of earlier neural processing (P100 and N170) abnormalities. Consistent with their previous investigation, findings suggest a reduced ability to correctly identify emotional facial expressions among alcoholics and atypical neural activation at decisional processing stages. In contrast, these results point to altered neural activity that might be valence dependent. However, given that the study was designed to address multimodal processing and stimulus presentation was restricted to two emotions, no formal conclusions can be made as of yet. Nonetheless, the results obtained from these preliminary experiments provide a useful foundation for future investigations of AUD.

Explicit emotion processing has also been studied in long-term abstinent (≥ 6 months) alcoholics, suggesting persistent behavioral impairment and atypical neural activation. Fein and colleagues (2010) demonstrated these neurobehavioral deficits with maximum intensity happy and sad facial expressions, for which long-term abstinent alcoholics showed longer reaction times and delayed latency of the P160, a component elicited by attended and unattended facial stimuli. In this particular study, neurobehavioral deficits did not differ by emotion type and measures of accuracy, P160 amplitude, and P3 characteristics did not show any alcohol-related compromise. These findings might suggest that EFE processing deficits persist in long-term abstinence, yet,

neural inefficiency might present differently than that which is observed in recent abstinence.

Importantly, evidence exists for some improvement in EFE processing with long-term abstinence (Kornreich et al., 2001b). Abstinence-dependent recovery of emotion processing abilities might suggest that impairment is at least partially attributable to the deleterious effects of chronic heavy alcohol use, and not entirely a function of an AUD-related predisposition (Uekermann & Daum, 2008). Therefore, detailed characterization of emotion processing in alcoholism has the potential to inform treatment efforts and facilitate recovery. The inconsistencies noted above emphasize the need for further inquiry as to whether or not differential deficits exist according to valence and emotion type and to better characterize the component processes implicated.

The relationship between EFE processing and interpersonal problems also merits greater attention. Kornreich and colleagues (2002) have previously reported a relationship between EFE processing and interpersonal functioning, as well as the potential for interpersonal difficulties to increase risk of relapse during early- and mid-term abstinence. Despite these compelling preliminary data, direct investigation of the association between interpersonal functioning and emotion processing is surprisingly scarce in the AUD-relevant literature.

Among AUD-focused investigations of EFE processing, interpersonal problems have been predominantly assessed by Maurage and colleagues. In their investigations, interpersonal functioning was evaluated with the Inventory of Interpersonal Problems (IIP; Horowitz et al., 1988). The IIP assesses the quantity and quality of social interactions and personal relationships, providing measures of overall interpersonal

problems (overall scores) and difficulty within discrete interpersonal domains (subscale scores). Using this inventory, the investigation of interpersonal functioning in Maurage and colleagues' behavioral and ERP studies (noted above) have yielded inconsistent findings. Some data suggest equivalent overall IIP scores between recently abstinent alcoholics and community controls (Maurage et al., 2007b, 2007a, 2008a). Other assessments have revealed higher IIP scores (i.e. higher levels of interpersonal difficulty) among alcoholics, both overall (Maurage et al., 2008c, 2009) and on specific subscales (Maurage et al., 2008d, 2009).

In one of these reports, Maurage and colleagues (2009) investigated the relationship between interpersonal functioning and emotion identification. For this study, a variety of emotionally-laden stimuli (i.e., faces, postures, voices, short stories) were presented and participants rated each stimulus on multiple Likert scales to indicate the emotions they believed to be depicted. Average ratings across all emotional stimuli were assessed for correlations with IIP scores, revealing a relationship between emotion processing and the self-control-problems subscale of the IIP among alcoholics (inventory and subscales detailed in Chapter 2, Methods). More specifically, greater difficulty with self-control, in the context of interpersonal relationships, was associated with an overall tendency to judge emotionally-laden stimuli as depicting a greater degree of anger and threat. Higher scores on this subscale have also been shown to correlate with greater difficulty identifying endogenous emotional states (i.e. self-experienced emotions; Maurage et al., 2008d). Importantly, the correlations noted here were specifically observed among alcoholics, and significant group differences (AUD vs. CC) for ERP and behavioral measures have still been observed when between-group

variability in interpersonal problems are controlled for (Maurage et al., 2008c). However, additional research is needed among other investigative teams and AUD populations before any clear conclusions can be made about the association between EFE processing and interpersonal functioning. Given the suggested relationship between interpersonal difficulties and early-recovery outcomes, further characterization can provide significant insight not only to our understanding of emotion processing in AUD populations, but also to our understanding of the components that impact recovery.

Summary

The prevalence of alcoholism continues to surpass all other substance use disorders (CBHSQ, 2015b), with an estimated 16.3 million American adults meeting criteria for a current alcohol use disorder (SAMHSA, 2014). Acknowledging alcohol's individual and societal impact, several decades of scientific research have been directed toward better understanding the deleterious effects of chronic heavy alcohol use. A substantial literature has detailed cognitive processing impairments in populations with alcohol use disorders and, more recently, investigations have begun to address the domain of emotion processing. Taken together, preliminary evidence exists for an emotion processing deficit in alcoholism. Although behavioral impairment is not always observed, several studies demonstrate atypical EFE processing, including reduced ability to accurately identify emotions and overestimation of the emotional intensity perceived in facial expressions. A growing literature has also begun to elucidate the corresponding neural systems and component processes implicated in alcohol-related emotion identification difficulties. Yet, the exact nature of this deficit and the factors associated with it merit further investigation. In particular, valence and emotion specific findings require clarification. If a deficit exists, and is specific to

negatively valenced emotions in general or one emotion in particular (e.g., anger), this can have important implications for therapeutic strategies. Assessing the relationship between these emotion identification difficulties and various facets of interpersonal functioning might also advance our understanding of emotion processing in alcoholism, thereby informing treatment efforts aimed at successful rehabilitation.

CHAPTER 2
STUDY AIMS AND METHODS

Study Aims

In an effort to contribute to this growing literature and elucidate some of the unresolved issues, the current study examined neurobehavioral indices of EFE processing in alcohol dependent treatment seekers, relative to healthy, non-alcoholic community controls.

Behavioral investigation of EFE processing was conducted using measures of accuracy and reaction time for an emotion judgement task. Because EFE processing impairments could be attributable to global visuospatial processing deficits and/or general psychomotor slowing, performance measures were also assessed for control tasks (sex judgement task and simple reaction time task; detailed in subsequent sections). Importantly, evidence suggests that performance-based deficits observed in abstinent alcoholics may be the result of inefficient processing (Glenn & Parsons, 1990, 1992). Efficiency of the processes that underlie emotion identification can be investigated in several ways; our laboratory has used speed-accuracy tradeoffs as one way to assess this (e.g., Hoffman et al., 2015; Nixon et al., 2007). With this measure, high levels of accuracy accompanied by fast reaction times reflect efficient processing (Kaplan, 1988). Trade-offs are sometimes observed in abstinent alcoholics such that individuals may slow responses to achieve greater accuracy, or respond more quickly, but at the cost of accurate performance (Glenn & Parsons, 1990, 1992). Thus, in an effort to apply a process oriented approach to these data, behavioral measures were also assessed for speed-accuracy trade-offs via efficiency ratios (% accuracy / mean reaction time for accurate trials).

Consistent with this approach, event related potentials (ERPs) were used to investigate the integrity of underlying processes at the neural level. Based on previous research, two endogenously driven components were investigated: 1) N170 to assess neural responses associated with higher-order perceptual processing of faces, and 2) the P3 to examine processes linked to the decisional stages of stimulus evaluation (here, emotion judgement). The N170 is a negative going waveform that occurs between approximately 130 and 200 ms after stimulus onset and is maximal at occipito-temporal sites. Multiple cortical regions are thought to contribute to N170 activation, but the lateral portion of the posterior fusiform gyrus and the anterior/middle fusiform gyrus have been suggested as dominant sources (Rossion & Jacques, 2011). P3 occurs at relatively later processing stages, approximately 300-500 ms post stimulus presentation (Campanella et al., 2009, Luck et al., 2014). This positive going waveform is maximal at parietal electrodes (Luck, 2005; Knight, 1996); the medial temporal lobe and the temporal parietal junction are suggested sources of P3 elicitation (Polich, 2007). In addition to its association with decisional processing stages, P3 component activation might also reflect efficiency of stimulus processing (Campanella et al., 2009). Some investigators suggest that P3 component activation is accompanied by widespread neural inhibition of ongoing activity; thereby, increasing the resources available for further processing of task relevant stimuli (Campanella et al., 2009). Previous investigations have shown N170 and P3 component sensitivity to emotion (relative to neutral expression; for a review, see Hajcak et al., 2012) and some suggest that activation might be modulated by emotion type. For example, relative to happy expressions, sad and angry expressions have elicited delayed N170 (Batty & Taylor,

2003) and P3 latency (Maurage et al., 2008d), respectively. Recorded during the emotion judgement task and sex judgement task, these components and their corresponding behavioral measures allowed us to extend a growing literature concerning emotion processing in alcoholism with the following project aims:

Aim 1

Compare neurophysiology and behavior in alcohol dependent treatment seekers (ADs) and non-alcoholic community controls (CCs) using an emotion judgement task that required identification of happy, angry, and sad facial expressions. Consistent with previous investigations, we predicted Hypothesis 1) Emotion processing would be altered in ADs. More specifically, we predicted that ADs would exhibit poorer task performance (on at least one behavioral measure) and neurophysiological alterations, including attenuated amplitudes and possibly delayed latencies. Concerning neurophysiological alterations, we asked Empirical Question 1) whether atypical activation would be observed at earlier perceptual processing stages, later decisional processing stages, or both.

Furthermore, evidence from a recent investigation (Maurage et al., 2008b) suggests that alcohol-related neurophysiological alterations and behavioral deficits in facial processing might be specific to emotion and not generalizable to other domains of face discrimination (e.g., sex, race, age). Therefore, we predicted Hypothesis 2) Behavioral and/or neurophysiological alterations in ADs would be specific to emotion judgement processing, such that dependent measures would be similar between ADs and CCs when task performance required non-emotional face discrimination (i.e. sex judgement task).

A primary objective of the current investigation was to shed light on whether or not abstinent alcoholics exhibit a differential deficit across various emotions. Mixed findings regarding the impact of valence and emotion type restricted a sufficient hypothesis. Therefore, we asked Empirical Question 2) If neurobehavioral indices of atypical emotion processing would be moderated by emotion type (happy vs. angry vs. sad).

Aim 2

Examine the relationship between emotion processing and interpersonal functioning among ADs and CCs. Given preliminary evidence suggesting a relationship between emotional facial expression processing and interpersonal functioning, we hypothesized that Hypothesis 3) behavioral measures of emotion processing would correlate with the degree of self-reported interpersonal problems. More specifically, we predicted that poorer performance on the emotion judgement task would be associated with greater interpersonal difficulty. Furthermore, we asked Empirical Question 3) Whether significant relationships were accounted for by a particular interpersonal domain and Empirical Question 4) if these relationships differed between ADs and CCs.

Summary of Aims

In summary, the current study assessed the neurobehavioral correlates of emotion processing in alcohol dependent treatment seekers relative to non-alcoholic controls. Using neurophysiological and behavioral measures of emotional facial expression processing, the investigation primarily aimed to contribute to this growing literature in two ways. First, we set out to replicate previous research demonstrating atypical emotion processing in alcoholism, and to identify its neurophysiological

characteristics at earlier vs. later processing stages, specificity to emotional content, and selectivity according to emotion type. Second, we intended to assess the relationship between emotion processing and interpersonal functioning.

Methods

A description of the participants, experimental procedures, data acquisition and analysis is detailed below. All procedures were approved by the University of Florida Health Science Center Institutional Review Board (protocol #125-2013). Participants provided written informed consent prior to the collection of screening and testing data and were compensated for participating.

Participants

A total of 73 volunteers participated in the current investigation, including 34 alcohol dependent inpatient treatment seekers (AD; 28 men and 6 women) recruited from residential substance use treatment facilities and 39 healthy, non-alcoholic community controls (CC; 15 men and 24 women) recruited via newspaper ads and flyers. Participants in both groups completed two screening sessions to determine eligibility.

As part of the initial screening, participants completed paper-pencil questionnaires and cognitive assessments. Inventories concerned 1) demographics, 2) negative affect, including assessments of depression (Beck Depression Inventory-II (BDI-II); Beck et al., 1996) and anxiety (State Anxiety Inventory (STAI); Spielberger, 1983), 3) premorbid intellectual ability (Shipley Institute of Living Scale-Verbal (SILS-V); Zachary, 1986), 4) familial history of alcohol problems, and 5) personal substance use histories, including brief assessments of chronicity, quantity and frequency of alcohol

use (Quantity Frequency Index (QFI); Cahalan et al., 1969). See Table 2-1 for further information regarding paper-pencil screening measures and exclusionary cutoffs.

Individuals who continued to qualify participated in the second screening session, during which vision was evaluated via Snellen chart (20/40 or better corrected vision was required to meet task demands), self-reported medical histories (i.e. mental/physical health conditions and current medications) were obtained, and current/past psychiatric disorders were assessed using APA's Diagnostic and Statistical Manual for Mental Disorders. DSM 5 instrumentation was not available at the start of investigation. Therefore, Axis-I disorders were evaluated per DSM-IV criteria using the computerized Diagnostic Interview Schedule-IV (c-DIS; Robins et al., 2000; American Psychiatric Association Task Force on DSM-IV., 1994). Certain mental and physical health conditions were deemed exclusionary for both (AD and CC) groups. These included: 1) history of significant neurologic disorder/insult (e.g., stroke, epilepsy, coma, concussion), 2) medical conditions (e.g., HIV, Hepatitis C, chronic obstructive pulmonary disorder) or current use of medications (e.g., benzodiazepines, prescription opioids) that can interfere with neurobehavioral function, 3) regular use of inhalants (e.g., ether), 4) lifetime diagnosis of a psychotic disorder or bipolar disorder, 5) current diagnosis of major depression (unrelated to substance use among ADs), and 6) significant anxiety disorders, including lifetime diagnosis of obsessive compulsive disorder or agoraphobia and current diagnosis of panic disorder, social phobia, or post-traumatic stress disorder. Given the prevalence of anxious and depressive symptomatology among treatment populations, selection criteria related to these disorders were not further restricted in an effort to avoid recruiting a non-representative

sample and to promote study feasibility. For similar reasons, lifetime diagnosis of antisocial personality disorder and nicotine use / dependence were not exclusionary.

Overall sample selection criteria were accompanied by additional group specific criteria. In line with previous investigations, inpatient treatment seekers were required to meet DSM-IV criteria for current alcohol dependence (determined via c-DIS), be fully detoxified, and have between 21 and 90 days of abstinence. This window of alcohol sobriety was chosen to limit the direct effects of detoxification, constrain variability that might be introduced by longer-term abstinence, and ensure feasibility of participant recruitment within participating treatment facilities. Among CC participants, current or lifetime DSM-IV diagnosis of any substance dependence (excluding nicotine) was exclusionary. Furthermore, CCs were required to have a history of previous alcohol consumption but were not to exhibit drinking patterns that significantly exceeded moderate drinking guidelines (women: ≤ 7 drinks per week or 3 drinks within a 2 hr period; men: ≤ 14 drinks per week or 4 drinks within a 2 hr period; U.S. Department of Agriculture and U.S. Department of Health and Human Services, 2010).

It should be noted that DSM terminology and symptomatology for alcohol-related diagnoses have undergone recent revisions. Whereas the DSM-IV distinguishes between alcohol abuse and dependence, the DSM 5 consists of a single disorder (Alcohol Use Disorder), which ranges in severity (mild, moderate, severe) dependent upon the number of criteria endorsed. Furthermore, a craving or strong desire to use alcohol has been added to these criteria in the DSM 5 and recurrent alcohol-related legal problems have been removed. For the current study, DSM-IV diagnoses were used for two reasons: 1) As noted previously, the DSM 5 diagnostic instrument was not

available at the start of our investigation and 2) using DSM-IV criteria allowed us to relate our findings to an existing literature. Importantly, measures of alcohol craving were collected (detailed below in 'Self-Report Instruments') in an effort to generalize to the DSM-V.

Laboratory Protocol

Participants were instructed to abstain from sedatives and sleep aids 24 hours prior to their scheduled testing session and to avoid the use of sedating allergy medications on testing day. If participants typically consumed caffeine, they were advised to limit intake to one caffeinated beverage on the morning of testing. Transportation between the treatment facilities and our laboratory was provided for AD participants. Upon arrival, participants were queried about their adherence to pretesting guidelines and previously documented medication use was reviewed for potential changes. Additionally, a negative breath alcohol test, urine toxicology screen, and pregnancy test (for women of childbearing potential) were required for study participation. Participants who identified as current nicotine users were advised to continue typical use on the morning of testing to avoid potential withdrawal symptoms. The use of tobacco products is prohibited across the University of Florida campus, where testing was conducted. Given the potential for withdrawal symptoms to confound interpretation of study outcomes, participants who did not typically abstain from nicotine for the length of testing were administered a 7 mg nicotine patch upon arrival (but no sooner than 30 min after last use). Our laboratory's previous investigations (Ceballos et al., 2005; Nixon et al., 2007) suggest that this dose is well-tolerated across sexes and does not differentially affect performance in ADs and CCs. The nicotine patch was removed by laboratory personnel after testing and participants were instructed to refrain

from nicotine/tobacco use for several hours after its removal. As a precaution, blood pressure was measured periodically throughout the testing session. No adverse reactions were observed or reported.

After completion of pre-testing procedures, participants completed paper-pencil inventories and computerized tasks. These measures are detailed below.

Self-Report Instruments

Negative affect. The Beck Depression Inventory (BDI-II; Beck, 1996) and State Anxiety Inventory (STAI; Spielberger, 1983) were re-administered on the day of testing to evaluate depressive and anxious symptomatology, respectively. The BDI-II is a 21 item questionnaire for which summed scores reflect the severity of depressive symptoms experienced over the last two weeks. Levels of symptom severity and their corresponding range of BDI-II scores include: minimal (0-13); mild (14-19); moderate (20-28); severe (29-63). The STAI is a 20 item inventory for which participants report the intensity of their feelings at the present moment on a four-point scale. The weighted scores for each item are summed and the total score is then age and sex corrected. Standardized scores range from 34, indicating low state anxiety, to 112, indicative of high state anxiety.

Craving for alcohol. Alcohol craving was assessed among alcohol dependent participants with the Desires for Alcohol Questionnaire (DAQ; Kramer et al., 2010; Love et al., 1998). The DAQ consists of 14 items that address the desire to drink, positive reinforcement, negative reinforcement, and the ability to control drinking behaviors. Participants were instructed to respond for their heaviest period of past drinking. Scores range from 14 (no craving) to 70, with higher DAQ scores correspond to higher levels of alcohol craving.

Interpersonal problems. The Inventory of Interpersonal Problems-64 (IIP-64; Horowitz et al., 2000) was used to assess Interpersonal difficulties. Participants responded to each of the 64 items on a five-point Likert scale. This measure provides a total score (range:34-99) and scores for 8 sub-scales (scoring range: 34-99), with higher scores indicative of greater interpersonal difficulty. Sub-scales address the following domains of interpersonal problems: 1) domineering/controlling: difficulty releasing control and a self-identified tendency to be too controlling or manipulative; 2) vindictive/self-centered: hostile dominance, anger, irritability, distrust of and suspiciousness toward others; 3) cold/distant: minimal feelings of affection for and connection with others; 4) socially inhibited: anxiety, timidity, or embarrassment in social situations, as well as difficulty initiating social interactions and expressing feelings to others; 5) nonassertive: lack of self-confidence and self-esteem, difficulty dealing with social opposition, taking initiative, and being assertive; 6) overly accommodating: excessive submissiveness and difficulty denying the requests of others, as well as self-identification of being too gullible, exploitable, and easily taken advantage of; 7) self-sacrificing: socially desirable traits (e.g., sympathy) have become excessive and problematic, with the individual experiencing difficulty setting limits, maintaining boundaries, and putting their needs before the needs of others; 8) intrusive/needy: poor boundaries with other people, a strong need to feel engaged with and to hold the attention of others, difficulty being alone and inappropriate disclosure of personal information or interjection into matters that do not concern oneself. Overall and Sub-scale scores were sex corrected.

Computerized Tasks

To investigate emotional facial expression (EFE) processing, two face identification tasks, modeled after previously published electrophysiological paradigms (Maurage et al., 2008b), were administered: 1) an emotion judgement task (EJT) and 2) a sex judgement task (SJT) to ensure that EJT-related findings were specific to emotion and observed impairment was not due to a more global visuospatial processing deficit. Given that general psychomotor slowing is occasionally observed in abstinent alcoholics, a simple reaction time task (SRTT) was administered to control for group differences in psychomotor speed if necessary. For all tasks, stimuli were presented at the center of a monitor and participants were instructed to respond via button-press with the index finger of their dominant hand. Response speed and accuracy were equally emphasized as important for successful task performance. All testing took place in a private, sound-attenuated booth. Task descriptions are provided in the following sections and are outlined in the order in which they were administered (i.e. SRTT, SJT, EJT).

Simple reaction time task. The SRTT was administered to assess simple psychomotor speed. For this task, an asterisks (*) was presented at varying intervals (1000, 2500, and 5000 milliseconds (ms)) in a predetermined randomized order. The task consisted of 75 trials, with each stimulus presentation reflecting a single trial. Participants were instructed to respond via button press as soon as an asterisks appeared on the screen. The stimulus remained on the screen until the participant responded, at which point the asterisks was replaced by a blank screen and the participant awaited the next stimulus presentation. For each trial, the time interval

between asterisks onset and participant response was recorded. The dependent variable of interest was mean reaction time (milliseconds), averaged across all trials.

Sex judgement task and emotion judgement task. Face stimuli for both face identification tasks were derived using the Ekman stimulus set (Ekman & Friesen, 1976), the most common set of emotional facial expression stimuli utilized in the emotional face processing literature. Equal numbers of male and female posers, aged between 30 and 50 years, were selected in an effort to avoid sex and/or age related confounds. Task design and stimulus selection, detailed below, were guided by the work of Maurage and colleagues (2008b). For both face identification tasks, stimulus characteristics are reliably recognized and task difficulty is similar between emotion and sex judgement (Maurage et al., 2008b).

For the SJT, eight neutral expression faces (4 male and 4 female) were selected and male/female pairs were identified. Morphing software (Fantamorph Version 5.4.3, Deluxe Edition) was applied to each male/female pair to create face stimuli that varied in the proportion of masculine/feminine features. Four morph levels were created for each pair, with the resulting stimuli depicting the following male/female proportions: 1) 5% / 95% (i.e. 95F), 2) 35% / 65% (i.e. 65F), 3) 65% / 35% (i.e. 65M), and 4) 95% / 5% (i.e. 95M). This procedure resulted in a total of 16 sex-morphed face stimuli (4 pairs X 4 morph levels). See Figure 2-1 for an example of the stimuli obtained with these morphing procedures. To avoid participant expectation, sex-morphed faces were presented in a pseudo-random order. Randomization of stimulus presentation was achieved by dividing the SJT into 64 partitions, whereby each partition consisted of four trials (256 total trials) in which no single male/female pair or morph level was repeated.

These procedures resulted in a total of 64 stimuli per morph level. For each trial, a single face stimulus was presented for 1500 ms, during which participants were to indicate whether the face appeared more male (left button) or more female (right button) using a response pad. Each stimulus was followed by a 300 ms interstimulus interval indicated by a fixation cross (+), which informed the participant that the response window for that trial had ended. This task took approximately ten minutes to complete.

For the EJT, eight different posers (4 male and 4 female) were selected. In order to examine the effects of emotion type, task stimuli were developed using four facial expressions from each poser, including neutral, happy, angry, and sad expressions. Guided by the work of Maurage and colleagues (2008b), investigation was limited to three emotional facial expressions (EFEs) to avoid participant fatigue and stimulus overexposure. To ensure adequate task difficulty and avoid ceiling effects, within-poser morphing procedures were performed to create EFEs of varying intensities. For a given poser, each EFE was morphed with its respective neutral expression to represent 35%, 65%, and 95% of the target emotion (65%, 35%, and 5% neutral expression, respectively). These procedures resulted in 72 EFE stimuli (8 posers X 3 emotions X 3 morph levels). See Figure 2-2 for an example of the EFE stimuli obtained using these morphing procedures. EFE stimuli were presented in a predetermined pseudo-random order in a series of blocks. Within a single block, only two target emotions were presented and task demands required discrimination between these same two expressions. All possible two-emotion combinations (i.e. happy-angry, sad-angry, happy-sad) were each presented in five blocks. Thus, the EJT consisted of 15 blocks and 48 trials per block (8 posers X 2 emotions X 3 morph levels), resulting in a total of

720 trials (80 trials for any given emotion/morph combination). No single poser/emotion/morph stimulus combination was repeated within a given block. Prior to each block, participants were informed of the two emotions that were to be presented and their corresponding button assignment (left or right) on the response pad. For each trial, a single EFE stimulus was presented for 1500 ms, during which participants were to indicate which of two possible emotions was most prominently expressed by pressing the respective button. The EFE stimulus was followed by a 300 ms interstimulus interval indicated by a fixation cross (+), which informed the participant that the response window for that trial had ended. Button-press assignment (L/R) for a given emotion alternated across task blocks and the order of block presentation was counterbalanced between participants and within group (AD vs. CC). The EJT took approximately twenty-five minutes to complete.

For both tasks, behavioral measures of interest were percent accuracy, reaction time (milliseconds) for accurate trials, and efficiency ratios (% accurate / average reaction time for accurate trials).

Electrophysiology Recordings

The electroencephalogram (EEG) was recorded during the SJT and EJT in a sound-attenuated, electrically shielded booth (~6’ X 8’, Eckel Industries of Canada Limited, Morrisburg, Ontario). Participants were fitted with an elastic EEG cap (Electro-Cap International, Eaton, OH) according to cranial circumference and nasion-to-inion measurements, after completing the paper-pencil assessments and the SRTT. Data were collected using a 64-electrode array mounted in an expanded International 10-20 System configuration, linked earlobe references, and a mid-forehead ground. Electrodes were placed on the supraorbital and infraorbital perimeter of the left eye to

monitor eye blinks and movements. Electrode impedances were maintained below 10 kOhms with conductive gel, individually inserted into each electrode using blunted-tipped syringes. The continuous EEG was amplified at a gain of 10,000x and subjected to an analog 0.1 – 100 Hz band-pass filter (Neuroscan 4.4 Acquire, Compumedics USA, Charlotte, NC). Data were analog-to-digital converted at a sampling rate of 1000 Hz. During recording sessions, participants were seated at a table with a mounted chin rest to minimize artifacts and stimuli were presented 70 cm in front of them on a 17" LCD monitor using E-Prime software (Psychology Software Tools, Inc., Sharpsburg, PA).

Data Analysis

All statistical analyses were performed using SAS Version 9.3 (SAS Institute, Inc., Cary, NC). Statistical significance was defined as $p \leq 0.05$. Adjustments for heteroscedasticity and multiple comparisons (Bonferroni post-hoc corrections) were applied where appropriate.

Participant Characteristics

Data concerning demographics, negative affective, and substance use histories were analyzed for group differences, between alcohol-dependent (AD) and community control (CC) participants, using independent t-tests and chi-square analyses. Where appropriate, descriptive and dependent variables of interest were subject to Pearson correlations to identify potentially confounding relationships.

Behavioral Analyses

SRTT performance was assessed for group differences using a t-test. Separate generalized linear mixed models (GLMM) were used to analyze behavioral outcomes for the SJT and EJT. The use of GLMM, a particularly powerful and flexible model, allowed for the application of data-driven covariance structures and more accurate statistical

analysis when violations of normality and homoscedasticity were observed. Within these models, group (2; CC vs. AD) was designated as the between-participants factor for both tasks. For the SJT, morph-level (4) was designated as the within-participant factor. Two within-participant factors were defined for the EJT, including emotion (3) and morph level (3). Although SJT and EJT within-participant outcomes were not the focus of this investigation, within-participant findings are reported in the results to provide a means of between-study comparisons for general task-related effects.

ERPs

EEG records were processed offline using EEGLAB Toolbox (Delorme & Makeig, 2004). Data were subject to a 30 Hz low-pass digital filter and 24 dB attenuation. Epochs were defined within the continuous record, starting 200 ms prior to face stimulus onset (baseline) and ending 1499 ms after it. Trials with incorrect responses were eliminated. Epochs that contained gross artifacts (voltage recordings larger than ±150 μV) were rejected. Participants producing less than 40 percent of the total possible accepted epochs within a given block, for either the SJT (< 25 accepted epochs for any given morph level) or EJT (<32 accepted epochs for any given emotion/morph combination), were excluded from task-specific analyses. After participant exclusion (SJT: n=9, 3 CC and 6 AD; EJT: n=12, 6 CC and 6 AD), an average of 199.33 ± 32.55 SJT and 542.17 ± 88.58 EJT trials were deemed suitable for ERP component analysis. Remaining epochs were subjected to an independent component analysis (ICA; Jung et al., 2001) and an automated technique for identifying and removing artifacts (i.e. ADJUST; Mognon et al., 2011). For each participant, separate epochs were averaged and baseline corrected for the four morph levels of the SJT and for the nine emotion/morph combinations (e.g., happy expression at 65% intensity) of the EJT.

According to conventional ERP analysis procedures (Luck, 2014), N170 and P3 component coordinates, including measurement windows and electrode sites, were determined via visual examination of group-specific grand average waveforms and guided by the currently available literature. For both groups, P3 was measured between a post-stimulus onset measurement window of 350 to 500 ms. Visual examination of the grand averaged waveforms suggested group-dependent N170 latencies. Accordingly, measurement windows were defined separately for each group. N170 was measured in post-stimulus onset windows ranging from 110 to 180 ms for CCs and from 130 to 200 ms for ADs. Consistent with previous investigations (e.g., Maurage et al., 2008b), P3 was measured at PZ (midline electrode) and N170 was measured at T5 and T6 (contralateral temporal-occipital sites). Given that hemispheric differences in component elicitation were not a primary focus of this investigation, and that the T5 and T6 sites yielded similar outcomes for dependent measures of interest, N170 measures were averaged across the T5 and T6 electrode sites to avoid unnecessary complication of data interpretation. After measurement windows and sites were determined, individual mean amplitudes (i.e. average amplitude within a defined measurement window; Luck, 2014) and 50% area latencies (i.e. time from stimulus onset at which an epoch-defined waveform reaches the midpoint of its calculated total area under the curve; Luck, 2014) were obtained (EEGLAB Toolbox) for the N170 and P3 components. These measures were chosen over peak measures, as they are thought to be more reliable (e.g., less influenced by data filtering) and better suited to handle variability in noise level between groups (commonly observed in patient/control comparisons; for a more thorough review, see Luck, 2014).

Importantly, mean amplitude and fractional area latency, particularly those extracted from shorter duration components, are somewhat more sensitive to investigator-defined measurement windows than peak measures (Luck, 2014). In an effort to ensure that the components of interest were accurately captured across participants, N170 and P3 amplitude were assessed for outliers (±2 SD from the mean), separately, for each task and within group. When outliers were identified, their waveforms were examined to determine whether or not the participant's component of interest occurred within the designated measurement window. When task- and component-specific latencies clearly occurred outside those defined via grand average waveforms, participants were excluded from the corresponding analysis. As a result, 3 and 6 participants were excluded from N170 analyses for the SJT and EJT, respectively. No participants were excluded from SJT or EJT P3 analyses. Although participant exclusion is less than ideal, the documented benefits of mean amplitude and fractional area latency drove the decision to move forward with these measures in ERP analyses.

N170 and P3 amplitudes, as well as P3 latencies, were individually assessed with separate GLMM analyses for the SJT and EJT. Similar to performance-based analyses, group (2; CC vs. AD) was designated as the between-participants factor for both tasks and within-participant factors were defined as morph-level (4) for the SJT, and emotion (3) and morph level (3) for the EJT. As mentioned above, visual inspection of the grand average waveforms guided the use of different N170 measurement windows between groups. Therefore, N170 latency was analyzed within group; Separate analyses were conducted for the SJT and EJT using GLMMs that contained

within-participant factors only. Similar to performance measures, within-participant effects for ERP measures were not the focus of investigation, but are provided in the results for readers interested in general task-related outcomes.

Interpersonal Difficulties

Overall IIP-64 scores (i.e. total scores) were investigated for group (AD vs. CC) differences with a one-way ANOVA. Mixed effects ANOVA was used to test for group effects on IIP-64 subscale scores, with group (2) as the between-participants factor and subscale scores (8) as within-participant factors. Potential relationships between interpersonal problems and behavioral EJT measures were assessed with Pearson correlations. Correlation-based analyses were initially conducted for total IIP scores and all nine emotion/morph combinations, within group. Where significant relationships were observed for either group, Pearson correlation coefficients were then calculated between the respective behavioral measure and the IIP subscales to determine if relationships could be accounted for by a particular interpersonal domain. Significant relationships observed among CCs and/or ADs, were also assessed for group differences using Fisher's Z score transformations (i.e. differences between group-specific correlation coefficients).

General Considerations

Acknowledging the potential for other factors to impact group-related outcomes, variables that have previously been shown to influence emotion processing and/or general neurobehavioral function were given additional consideration. Although addressing all potential modulating factors is beyond the scope of this report, the current study focused on two variables, sex and nicotine use.

Importantly, studies suggest that sex has the potential to modulate emotion processing in healthy populations (see Hamann & Canli, 2004 for a review) and influence alcohol-related neurobehavioral compromise in various cognitive domains (see Nixon et al., 2014 for a review). Although a direct investigation of sex was not feasible within the confines of the current study's sample characteristics, sex was included as a covariate in SJT and EJT performance- and ERP-based analyses, whenever possible, to control for its potential influence on study outcomes. Accordingly, all SJT and EJT GLMMs noted above ('Behavioral Analyses' and 'ERPs') included sex as a covariate.

Another important factor with the potential to influence neurobehavioral function is nicotine use (see Durazzo et al., 2010 for a review). Given that the current study's sample included nicotine users and non-users, analyses were specifically conducted to determine whether or not nicotine-use had an effect on the dependent variables of interest. Overall task performance as well as N170 and P3 amplitude and latency were individually assessed for potential differences between users and non-users. Analyses of covariance (ANCOVAs) were conducted separately for the SJT and EJT with nicotine-use status (current use vs. no use) designated as the between-participants factor. Given the limited number of CC participants who endorsed current nicotine use, group (CC vs. AD) was included in the model as a covariate rather than an independent variable. Consistent with other SJT and EJT analyses, sex was added to the model as an additional covariate. Nicotine-use status did not emerge as a significant factor in any SJT or EJT performance- or ERP- based analysis (all ps>0.05). Therefore, this variable was not given any further consideration.

Table 2-1. Screening Measures and Exclusionary Cutoffs

Screening Measure	Assessment	Exclusionary Cutoff [f]
Age	-	< 25 or > 59 years
Education	-	< 10 or > 16 years
Beck Depression Inventory (BDI-II)[a]	Depressive symptomatology	> 28 (i.e. severe symptomatology)
State Anxiety Inventory (STAI)[b]	State anxiety	Not exclusionary
Shipley Institute of Living Scale – Verbal (SILS-V)[c]	Verbal ability	< 13.1
Multi-Generational Family Tree of Substance Use [d]	Density of familial alcohol problems	Not exclusionary
Quantity Frequency Index (QFI)[e]	Avg. oz. of absolute ethanol consumed per day in the 6 months prior to screening (CC) or treatment (AD)	AD: QFI = 0 (indicates > 90 days abstinent) CC: Not exclusionary

[a] Beck, 1996, [b] Spielberger, 1983, [c] Zachary, 1986, [d] adapted from Mann et al., 1985; To calculate density, weighted scores are assigned to primary (1) and secondary (0.5) members with alcohol problems and divided by the total number of family members, [e] Cahalan et. al., 1969, [f] Exclusionary cutoffs apply to all participants unless otherwise noted. AD = alcohol dependent group. CC = community control group

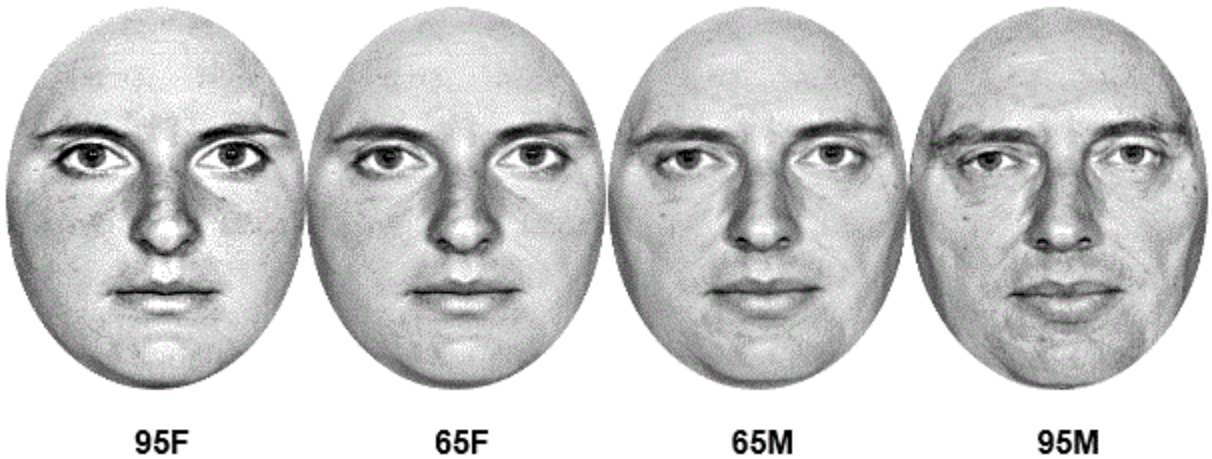

Figure 2-1. Sex Judgement Task: Illustration of Sex Morphed Stimuli. Figure depicts an example of the continuum from female to male face at the four morph levels presented in the Sex Judgement Task. Values indicate the proportion (%) of the dominant sex (F = female; M = male) depicted in the sex morphed stimulus. Face stimuli adapted by Neurocognitive Laboratory (University of Florida; PI: S.J. Nixon), from Ekman Stimulus Set (Ekman & Friesen, 1976).

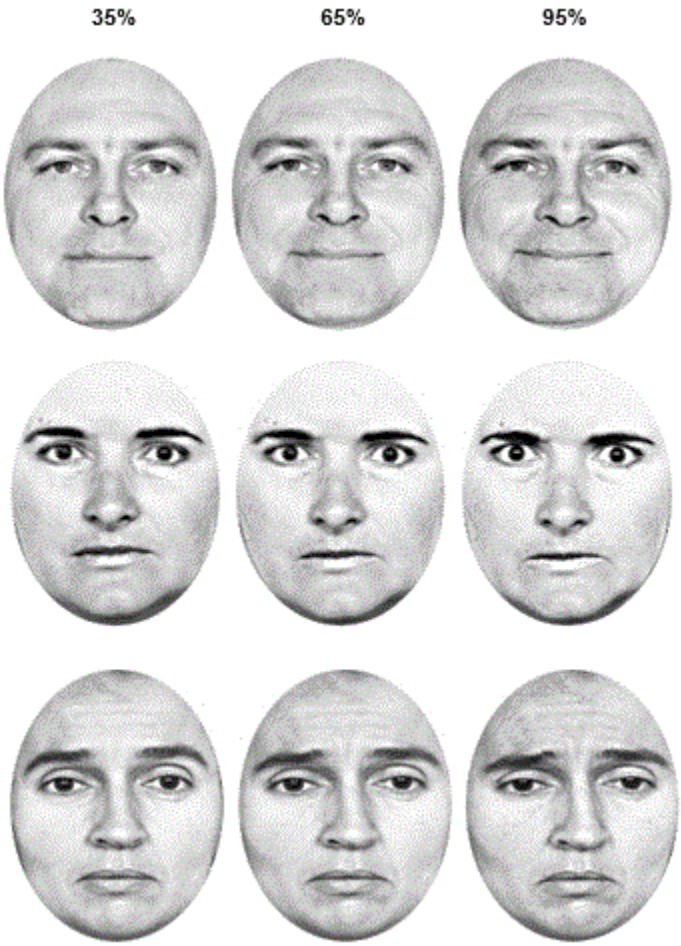

Figure 2-2. Emotion Judgement Task: Illustration of Morphed Emotional Facial Expression Stimuli. Figure depicts an example of the EFE stimuli developed via morphing procedures and used in the Emotion Judgement Task. This task consisted of three emotional expressions (happiness (top row), anger (middle row), and sadness (bottom row)), presented at three intensity levels. Values indicate the proportion of emotion depicted in each emotional/neutral expression morphed stimulus (35, 65, and 95 percent intensity). Face stimuli adapted by Neurocognitive Laboratory (University of Florida; PI: S.J. Nixon), from Ekman Stimulus Set (Ekman & Friesen, 1976).

CHAPTER 3
RESULTS

Descriptive Variables

Demographic and affective measures are presented by group in Table 3-1. Overall, participants were between the ages of 25 to 59 years (M=42.41, SD=10.75) and had completed 11 to 16 years of education (M=14.14, SD=1.67). The majority of participants were Caucasian (78%). The sample also consisted of African Americans (18%) and individuals endorsing 'other' race (4%). Affective measures, collected on the day of laboratory testing, suggested relatively low levels of state anxiety (STAI; M=43.86, SD=8.82) and depressive symptomatology (BDI-II; M=6.07, SD=6.51) across participants.

When demographic and affective measures were compared between groups, significant differences emerged for educational achievement ($t(71)=3.24$, $p=0.002$) and depressive symptomatology ($t(71)=3.38$, $p=0.001$). Relative to AD participants, CCs had approximately one additional year of education and scored an average of 5 points lower on the BDI-II. Consistent with inclusionary/exclusionary participant criteria, mean BDI-II scores for both groups indicated subclinical, minimal levels of depressive symptomatology. Given that these group differences were not particularly meaningful and neither education, nor the BDI-II, significantly correlated with dependent measures of interest, these variables were not given further consideration. Analyses also revealed an unequal distribution of male/female sex between CCs and ADs ($\chi^2=14.45$, $p=0.0001$). As discussed in the Methods, the data analysis strategy was designed to account for the potential influence of sex on dependent measures of interest. See

'Additional Considerations' for further detail. All other demographic and affective measures were equivalent between groups.

Means and standard deviations for key alcohol-related measures are presented for the AD group in Table 3-2. On average, ADs had completed two formal substance-use treatments, reported a 15-year duration of alcohol-use problems, and had a mean QFI reflecting pre-treatment consumption of approximately 26 standard drinks per day. As expected, mean QFI among CCs (M=0.30, SD=0.41; Range=0.00-2.21) was significantly lower ($t(71)=8.63$, $p<0.0001$), reflecting an average of less than one standard drink consumed per day. Analyses also indicated a higher density of familial alcohol problems among ADs ($M_{density}=0.35$, SD=0.17; Range=0.06-0.67), relative to CCs ($M_{density}=0.10$, SD=0.11; Range=0.00-0.33; $t(50)=6.26$, $p<0.0001$). At the time of task administration, ADs had between 22 and 68 days of alcohol-related abstinence.

Regarding the use of other substances, 82% (n=28) of ADs endorsed the concurrent use of one or more drugs (excluding nicotine) in the six months prior to treatment. The substances most commonly reported among concurrent drug users included marijuana (44%, n=15) and opioids (35%, n=12). Stimulant- (cocaine: 18%, n=6; amphetamines: 12%, n=4), sedative- (benzodiazepines: 15%, n=5; muscle relaxers: 3%, n=1), and hallucinogen- (3%, n=1) use was also reported. Four CC participants endorsed marijuana use in the six months prior to study participation. Consistent with inclusionary/exclusionary criteria, all participants tested negative for the presence of illicit substances on testing day. Current nicotine use was more prevalent among the AD group (76%, n=26) than the CC group (10%, n=4; $\chi^2=43.46$, $p<0.0001$). Importantly, planned analyses suggested no significant effect of nicotine use on

neurobehavioral measures of interest. Consequently, this variable was not considered in subsequent analyses (more information available in 'Methods: Additional Considerations').

Neurobehavioral Measures of Task Performance

Given the investigational focus on between-group comparisons, within-participant effects for the SJT and EJT (i.e. morph and emotion) are not reported here. The following sections detail group-related neurobehavioral outcomes.

Simple Reaction Time Task

Analyses suggested equivalent SRTT performance between AD (M=481.10, SD=75.28 ms) and CC (M=482.80, SD=82.10 ms) groups ($p>0.05$). Therefore, it was not necessary to control for simple psychomotor abilities when assessing SJT or EJT performance.

Sex Judgement Task

Behavior. SJT performance measures are presented by group and morph-level in Table 3-3. No significant main effects or interactions involving group were observed for any behavioral measure of interest.

ERPs. ERP measures for the SJT are presented by group and morph level in Table 3-4. No significant main effects or interactions involving group were observed for N170 amplitude or P3 amplitude or latency. Within group analysis of N170 latency suggested an effect of morph among CCs ($F(3, 31)=3.57$, $p=0.03$). However, after correcting for multiple comparisons, posthoc analyses failed to reveal a significant difference between any morph level ($ps>0.17$). No significant findings emerged when N170 latency was analyzed within ADs.

Emotion Judgement Task

Behavior. EJT performance measures are presented by group and emotion, within each morph-level, in Table 3-3. Group-related main effect and interaction terms produced by overall GLMM analysis of accuracy, reaction time, and efficiency did not fully achieve statistical significance (ps>0.11). However, examination of group means suggested a potential difference in EJT accuracy that might have been concealed due to relatively small sample sizes and particularly complex statistical models. In an effort to address this suspected lack of statistical power and adequately investigate the primary research questions of interest, EJT performance variables were reassessed with the most ambiguous morph level (35%) excluded from statistical models (i.e. follow-up analysis with a 2 (group) X 3 (emotion) X 2 (morph) GLMM).

Using this method, findings revealed a significant effect of group ($F(1, 70)=3.88$, $p=0.05$), thereby confirming the current investigation's primary hypothesis. Posthoc comparisons suggested less accurate EFE identification among ADs (overall M=90.20, SD=5.73), relative to CCs (overall M=92.11, SD=4.18), across all emotions and both morph levels (Figure 3-1). Interestingly, no group by emotion, group by morph or group by emotion by morph interactions were revealed. However, examination of the GLMM estimated differences between group means suggested that the anger condition might have primarily driven the observed group main effect. Anger produced the largest mean difference (MΔ) at both the 65% (angry: MΔ=4.45%; happy: MΔ=1.65%; sad: MΔ=0.49%) and 95% morph levels (angry: MΔ=2.91%; happy: MΔ=0.87%; sad: MΔ=1.10%).

ERPs. ERP measures for the EJT are presented by group and emotion within each morph-level in Table 3-5. Analyses revealed a main effect of group on P3

amplitude ($F(1, 59)=4.02$, $p=0.04$; Figure 3-2); Across all emotions and morph levels, P3 amplitude elicited in response to EFEs was significantly smaller among ADs (overall $M=5.56$, $SD=3.68$ μV), relative to CCs (overall $M=7.88$, $SD=3.64$ μV). Grand average waveforms, measured at electrode PZ, are presented by group and emotion in Figure 3-3. Given that ERP measures are more sensitive than behavioral measures in detecting subtle differences, it is not surprising that significant group-related effects emerged sans reduction of the statistical model. In other words, it was not necessary to eliminate the most ambiguous morph level from analyses; statistical power was adequate for detecting significant group differences with these relatively sensitive neurophysiological measures. Examination of the GLMM estimated differences between group means again suggested a more pronounced difference for anger. Although anger did not produce the largest mean difference within all morph levels, the estimated group difference for anger at the 65% morph level was larger than the estimates of all other emotion/morph combinations ($M\Delta_{A65}=1.65$ μV; $M\Delta_{H65}=0.95$ μV; $M\Delta_{S65}=1.40$ μV; $M\Delta_{A95}=1.29$ μV; $M\Delta_{H95}=1.56$ μV; $M\Delta_{S95}=1.31$ μV; $M\Delta_{A35}=0.94$ μV; $M\Delta_{H35}=1.44$ μV; $M\Delta_{S35}=0.97$ μV).

Regarding the other ERP measures, no significant main effects or interactions involving group were observed for N170 amplitude or P3 latency. Furthermore, within group analysis of N170 latency yielded similar outcomes for ADs and CCs; no significant effects emerged for emotion, morph, or their interaction in either group. N170 component characteristics, collapsed across emotion and morph, are depicted in grand average waveforms at electrode site T6 in Figure 3-4.

Interpersonal Functioning

One-way ANOVA conducted for overall score on the IIP-64 revealed a significant group effect ($F(1, 71)=13.17$, $p=0.0005$); Higher scores were observed among ADs relative to CCs. When IIP-64 subscale scores were assessed, mixed-effects ANOVA yielded an overall effect of group ($F(1, 71)=13.81$, $p=0.0004$). Detailed characterization of this effect suggested significant group differences for all eight of the IIP-64 subscale measures, (all $Fs(1, 71)>3$, $ps\leq0.05$), with ADs consistently exhibiting higher scores than CCs. Means, standard deviations, and statistics regarding these data are presented in Table 3-6 by group.

In an effort to limit the number of statistical procedures conducted in the current investigation, analyses addressing the relationship between IIP-64 scores and behavioral measures of EJT performance were restricted to the investigation of accuracy. This performance measure was selected over reaction time and efficiency given its relative sensitivity to group-related effects. Correlational analyses conducted within group for overall IIP-64 scores and EJT accuracy revealed group-dependent associations. No significant relationships were observed among CCs for any particular emotion/morph combination. Conversely, correlational analyses conducted among ADs revealed significant relationships between the IIP-64 and measures of accuracy that were specific to anger. In particular, higher overall scores on the IIP-64 were associated with less accurate identification of angry expressions presented at 65% ($r=-0.36$, $p=0.04$) and 95% ($r=-0.37$, $p=0.03$) emotional intensity. When accuracy for these two EJT stimuli were subsequently assessed for sub-scale specific relationships among ADs, significant associations were specifically observed for three scales. Accuracy for angry EFEs at the 65% ($r=-0.34$, $p=0.05$) and 95% ($r=-0.44$, $p=0.01$) morph levels

negatively correlated with the “intrusive/needy” sub-scale of the IIP-64. Additional correlations were observed between accuracy at the 65% morph level and the “nonassertive” sub-scale (r=-0.37, p=0.03), as well as the 95% morph level and the “overly-accommodating” subscale (r=-0.36, p=0.04). As expected, analyses performed among CCs yielded no significant correlations between angry EFEs and any of the IIP-64 sub-scales.

Comparison of group-specific correlation coefficients with Fisher’s Z score transformations revealed a significant difference between groups for the relationship between overall IIP-64 scores and accuracy for anger at the 65% morph level (CC: r=0.03; AD: r reported above; Z=1.63, p=0.05). Correlation coefficients involving anger at the 95% morph level (CC: r=-0.18; AD: r reported above) did not significantly differ between ADs and CCs (p=0.19). With regard to the four sub-scale correlations (reported above for ADs), statistically significant group differences were only observed for coefficients that characterized the relationship between the “intrusive/needy” sub-scale of the IIP-64 and accuracy for anger at the 65% morph level (CC: r=0.13; Z=1.96, p=0.03). All other group comparisons involving sub-scale coefficients yielded trend-level, albeit nonsignificant, results (0.11>ps>0.07).

Table 3-1. Demographic and Affective Measures (By Group)

Measure	CC (n=39) M (SD)	AD (n=34) M (SD)
Age (yrs.)	43.79 (12.12)	40.82 (8.84)
Education (yrs.)[c]	14.69 (1.56)	13.5 (1.58)
BDI-II[a, c]	3.74 (4.04)	8.74 (7.74)
STAI[b]	42.03 (7.06)	45.97 (10.19)
	% (n)	% (n)
Race		
Caucasian	74 (29)	82 (28)
African American	21 (8)	15 (5)
Other	5 (2)	3 (1)
Sex[c]		
Male	38 (15)	82 (28)
Female	62 (24)	18 (6)

[a] Beck Depression Inventory-II; values reported for testing day (Beck et al., 1996), [b] State Anxiety Inventory; values reported for testing day (Spielberger, 1983), [c] Significant effect of group. See text for more detail. AD = alcohol dependent group. CC = community control group

Table 3-2. Alcohol-Related Measures (Alcohol Dependent Participants)

Measure	M (SD)	Range
Total No. of Formal Substance Use Treatments	2.24 (1.33)	1-6
Chronicity of Alcohol problems (yrs.)	14.91 (10.90)	1-37
Density of Familial Alcohol Problems[a]	3.74 (4.04)	0.06-0.67
QFI[b]	15.69 (10.39)	0.37-45.82
DAQ[c]	42.03 (7.06)	22-69
Days of Sobriety on Testing Day[d]	41.00 (12.63)	22-68

[a] See Table 2-1 for information regarding derivation of this measure (adapted from Mann et al., 1985), [b] Quantity Frequency Index; 0.6 = 1 standard drink / day (adapted from Cahalan et al., 1969), [c] Desires for Alcohol Questionnaire (Kramer et al., 2010; Love et al., 1998), [d] Pertains specifically to alcohol

Table 3-3. Sex Judgement and Emotion Judgement: Task Performance (By Group)

Sex Judgement Task						
	CC			AD		
Morph[a]	ACC (%)	RT (ms)	EFF	ACC (%)	RT (ms)	EFF
F95	91.39 (9.49)	775.01 (78.73)	1.1959 (0.2032)	92.84 (9.92)	774.95 (102.61)	1.2222 (0.2202)
F65	83.79 (14.53)	814.21 (76.46)	1.0440 (0.2321)	85.97 (11.99)	813.87 (108.53)	1.0777 (0.2162)
M95	96.47 (5.60)	748.61 (90.22)	1.3104 (0.1959)	97.43 (3.85)	765.65 (90.04)	1.2891 (0.1572)
M65	84.22 (14.23)	855.78 (103.22)	1.0072 (0.2425)	84.07 (9.68)	879.20 (95.64)	0.9687 (0.1596)

Emotion Judgement Task						
Emotion and Morph[b, c]	CC			AD		
	ACC (%)	RT (ms)	EFF	ACC (%)	RT (ms)	EFF
H35	84.09 (9.46)	854.14 (105.05)	1.0041 (0.1984)	84.96 (10.69)	832.66 (84.75)	1.0340 (0.1824)
A35	65.39 (10.52)	897.25 (90.54)	0.7373 (0.1446)	64.92 (11.82)	890.06 (91.62)	0.7402 (0.1670)
S35	83.69 (6.71)	889.14 (70.45)	0.9490 (0.1225)	82.57 (7.92)	876.46 (84.98)	0.9500 (0.1243)
H65	97.07 (3.46)	746.66 (96.70)	1.3214 (0.1788)	95.56 (4.96)	732.16 (80.26)	1.3219 (0.1728)
A65	89.44 (6.88)	853.08 (82.01)	1.0603 (0.1502)	85.12 (10.67)	845.85 (87.18)	1.0165 (0.1605)
S65	87.95 (5.66)	829.06 (82.90)	1.0723 (0.1357)	87.59 (5.43)	820.73 (81.47)	1.0781 (0.1308)
H95	96.70 (3.40)	718.60 (93.59)	1.3677 (0.1826)	95.96 (4.18)	711.02 (79.16)	1.3680 (0.1791)
A95	92.98 (5.10)	816.74 (82.58)	1.1511 (0.1412)	90.21 (7.66)	805.92 (77.99)	1.1306 (0.1485)
S95	88.33 (6.53)	819.18 (84.22)	1.0914 (0.1516)	87.37 (6.56)	809.09 (82.05)	1.0916 (0.1430)

Table values shown are means (standard deviations) for accuracy ('Acc'), reaction time ('RT'), and efficiency ('EFF'), [a] CC: n=38; AD: n=33; Levels indicate the dominant sex portrayed in each sex-morphed stimulus (M = male; F = female) and the degree (%) to which that sex was depicted (e.g., F95 = 95% female / 5% male), [b] CC: n=39; AD: n=34; Levels denote the emotion (H = happy; A = angry; S = sad) and the intensity at which it was expressed in the respective face stimulus (e.g., H65 = 65% happy / 35% neutral expression), [c] Significant main effect of group for reduced-model analysis of accuracy (i.e. excluding emotions presented at the 35% morph level). See text for more detail. AD = alcohol dependent group. CC = community control group.

Table 3-4. Sex Judgement Task: Electrophysiological Results

	CC				AD			
	N170 (N=32)		P3 (n=35)		N170 (n=27)		P3 (n=27)	
Morph Level[a]	Amp (μV)	Lat[b] (ms)	Amp (μV)	Lat (ms)	Amp (μV)	Lat[b] (ms)	Amp (μV)	Lat (ms)
F95	0.61 (1.85)	147.59 (9.85)	5.73 (3.98)	434.69 (15.86)	1.20 (2.55)	163.78 (9.84)	4.00 (3.23)	429.67 (17.24)
F65	0.65 (1.99)	144.39 (11.75)	5.62 (3.77)	431.83 (19.38)	0.76 (2.67)	163.94 (10.36)	3.22 (3.14)	428.07 (17.77)
M95	0.54 (1.67)	144.14 (11.14)	5.52 (3.47)	431.26 (19.01)	1.39 (2.70)	163.24 (9.75)	3.79 (3.21)	431.26 (17.22)
M65	0.69 (1.93)	143.25 (11.47)	4.80 (3.72)	426.00 (17.51)	1.14 (2.36)	162.33 (9.90)	3.30 (2.81)	425.96 (17.93)

Table values shown are means (standard deviations) for component amplitudes ('Amp') and latencies ('Lat'), [a] Levels indicate the dominant sex portrayed in each sex-morphed stimulus (M = male; F = female) and the degree (%) to which that sex was depicted (e.g., F95 = sex-morphed stimuli depicting 95% female / 5% male), [b] N170 measurement windows differed between groups; comparison of group latencies is not appropriate. See text for more detail. AD = alcohol dependent group. CC = community control group

Table 3-5. Emotion Judgement Task: Electrophysiological Results

Emotion and Morph[a]	CC				AD			
	N170 (N=29)		P3 (n=33)		N170 (n=26)		P3 (n=28)	
	Amp (μV)	Lat[b] (ms)	Amp[c] (μV)	Lat (ms)	Amp (μV)	Lat[b] (ms)	Amp[c] (μV)	Lat (ms)
H35	1.54 (1.74)	144.45 (11.35)	7.54 (4.00)	431.61 (11.30)	1.08 (2.53)	164.60 (9.81)	5.06 (3.60)	428.82 (14.97)
A35	1.60 (1.76)	146.67 (12.10)	7.17 (3.40)	429.73 (9.08)	1.18 (2.82)	165.79 (10.22)	5.18 (3.95)	427.14 (15.26)
S35	1.41 (1.50)	144.60 (11.85)	6.74 (3.80)	430.73 (10.16)	1.40 (2.12)	164.87 (10.27)	4.74 (3.48)	429.17 (15.60)
H65	1.29 (1.79)	144.60 (10.09)	8.19 (3.87)	430.45 (9.46)	1.52 (1.99)	163.88 (10.21)	6.20 (4.22)	428.50 (10.25)
A65	1.66 (1.47)	146.84 (12.78)	8.07 (4.30)	431.18 (8.07)	1.48 (2.40)	164.33 (10.15)	5.38 (3.80)	432.54 (18.38)
S65	1.50 (1.76)	147.05 (11.74)	7.69 (3.73)	431.06 (9.78)	1.47 (2.37)	163.94 (10.24)	5.24 (3.72)	429.18 (14.12)
H95	1.61 (1.67)	144.14 (12.24)	9.12 (3.95)	430.73 (8.85)	1.34 (2.24)	161.42 (9.92)	6.50 (4.03)	433.54 (13.83)
A95	1.49 (1.72)	147.84 (11.70)	8.55 (4.04)	433.36 (10.42)	1.66 (2.16)	165.44 (10.21)	6.21 (4.02)	430.11 (11.65)
S95	1.70 (1.80)	145.03 (10.94)	7.88 (3.54)	432.18 (8.27)	1.47 (2.76)	163.73 (8.55)	5.52 (4.02)	430.32 (15.59)

Table values shown are means (standard deviations) for component amplitudes ('Amp') and latencies ('Lat'), [a] Levels denote the emotion (H = happy; A = angry; S = sad) and the intensity at which it was expressed in the respective face stimulus (e.g., H65 = stimulus depicting 65% happy and 35% neutral expression), [b] N170 measurement windows differed between groups; comparison of group latencies is not appropriate, [c] Significant main effect of group on P3 amplitude. See text for more detail. AD = alcohol dependent group. CC = community control group

Table 3-6. Inventory of Interpersonal Problems: Total and Subscale Scores (By Group)

IIP-64 Scale	CC	AD	Statistics[a]
Total Score	50.64 (9.51)	59.62 (11.62)	F(1, 71)=13.17, p=0.0005
Domineering / Controlling	49.51 (9.93)	59.74 (12.81)	F(1, 71)=14.72, p=0.0003
Vindictive / Self Centered	49.13 (9.15)	57.41 (10.49)	F(1, 71)=12.98, p=0.0006
Cold / Distant	51.21 (11.80)	56.97 (12.84)	F(1, 71)=4.00, p=0.05
Socially Inhibited	51.05 (11.14)	56.59 (12.69)	F(1, 71)=3.94, p=0.05
Nonassertive	51.82 (11.22)	57.82 (14.75)	F(1, 71)=3.89, p=0.05
Overly Accommodating	49.46 (8.58)	57.85 (11.19)	F(1, 71)=13.10, p=0.0005
Self-Sacrificing	51.67 (8.60)	58.74 (11.13)	F(1, 71)=9.35, p=0.003
Intrusive / Needy	50.46 (9.12)	58.32 (12.45)	F(1, 71)=9.63, p=0.003

Table values in center columns are group means (standard deviations) for IIP-64 (Horowitz et al., 2000) scores, [a] One-way ANOVA and mixed-effects ANOVA revealed a significant main effect of group for total score and for all sub-scale scores, respectively. See 'Methods' for detailed description of these sub-scales. AD = alcohol dependent group. CC = community control group

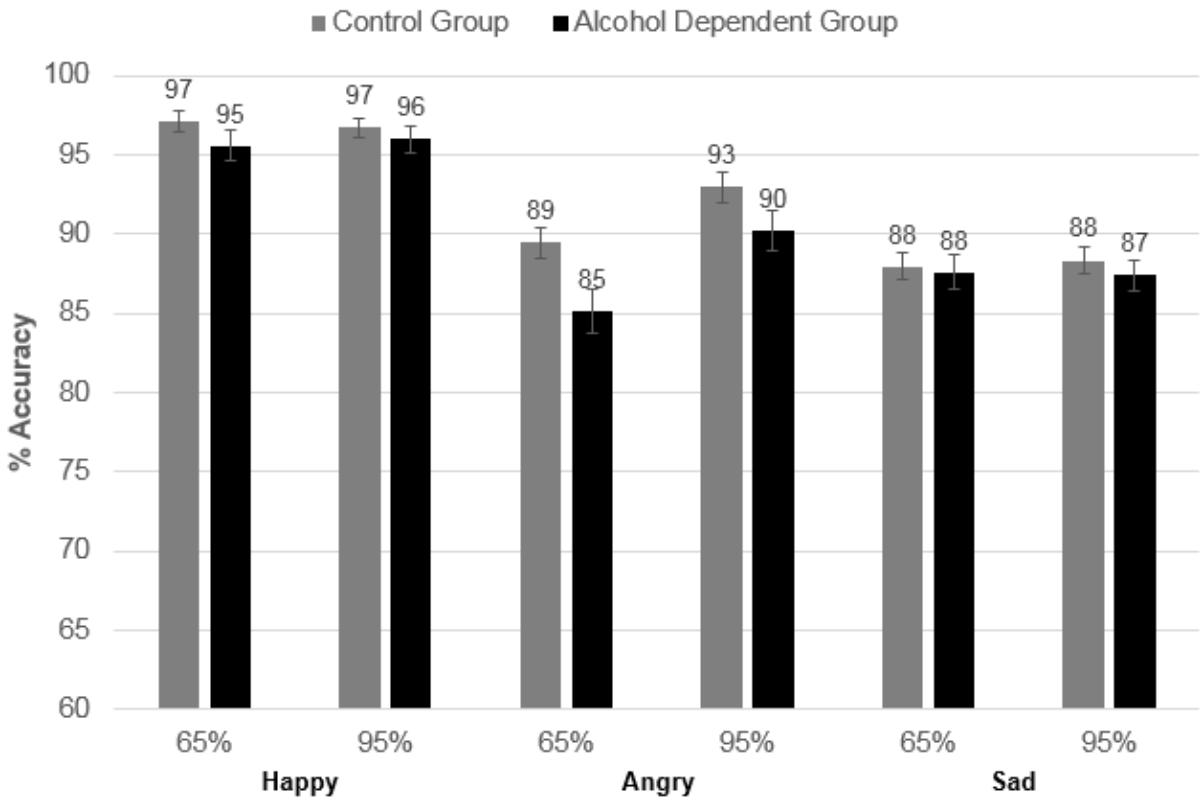

Figure 3-1. Emotion Judgement Task Accuracy: Group Main Effect. 2 (group: AD vs. CC) X 3 (emotion: happy, angry, Sad) X 2 (morph level: 65%, 95%) GLMM revealed less accurate performance among alcohol dependent participants, relative to community controls, across all emotions and morph levels ($F(1, 70)=3.88$, $p=0.05$). Error bars depict standard error.

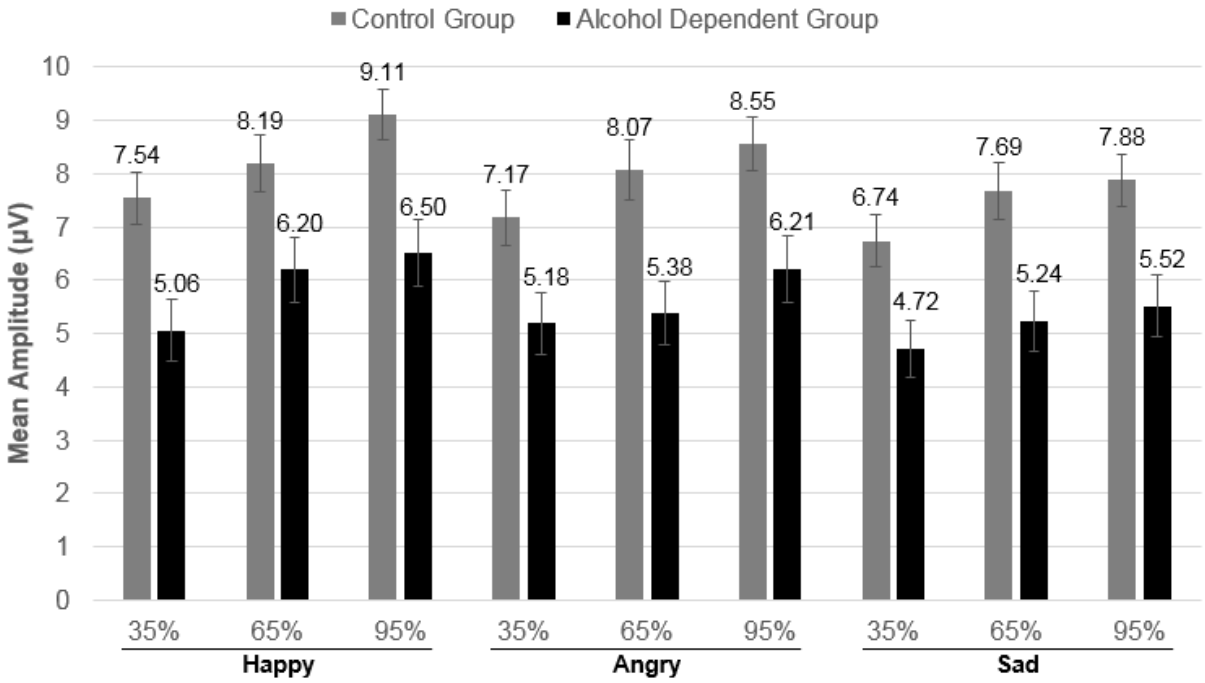

Figure 3-2. Emotion Judgement Task P3 Amplitude: Group Main Effect. 2 (group: AD vs. CC) X 3 (emotion: happy, angry, Sad) X 3 (morph level: 35%, 65%, 95%) GLMM revealed attenuated P3 amplitudes among alcohol dependent participants, relative to community controls, across all emotions and morph levels ($F(1, 59)=4.02$, $p=0.04$). Error bars depict standard error.

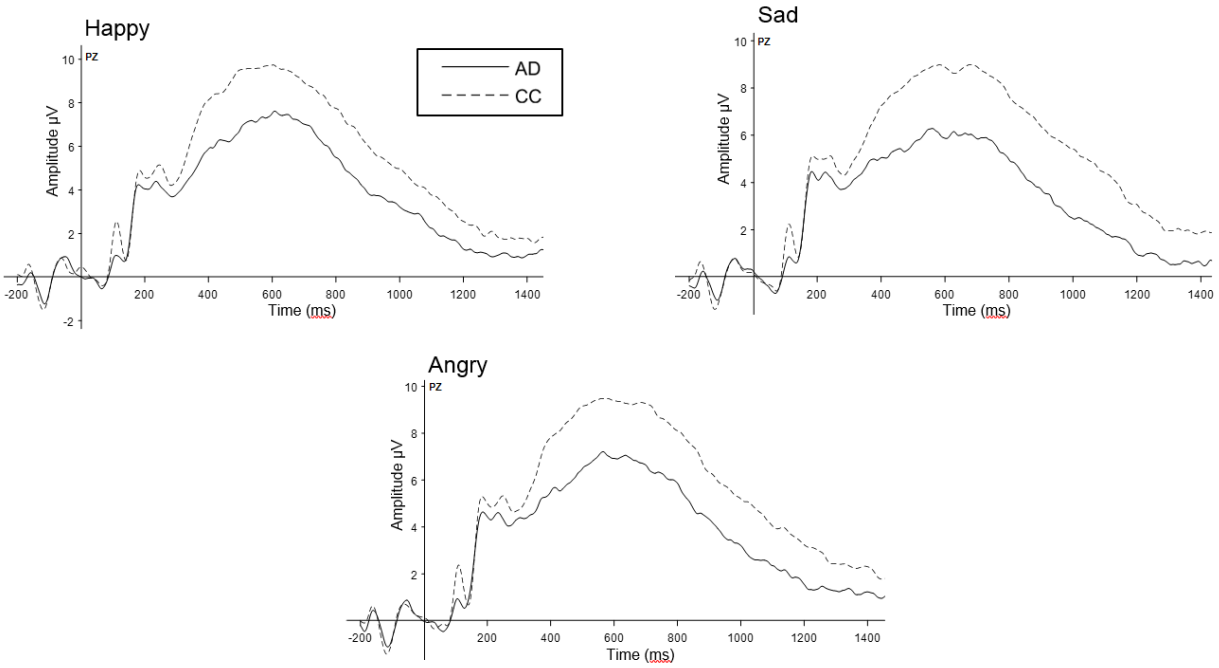

Figure 3-3. Grand Average EEG Waveforms: Emotion Judgement Task (Electrode PZ). Y-axis = mean amplitude. X-axis = time from stimulus onset. Note the positive going deflection (P3) in both groups beginning at approximately 350 ms. Investigation of P3 Amplitude (measured between 350-500 ms), revealed attenuated P3 amplitudes among alcohol dependent participants (AD) relative to community controls (CC), across all emotions and morph levels ($F(1, 59)=4.02$, $p=0.04$).

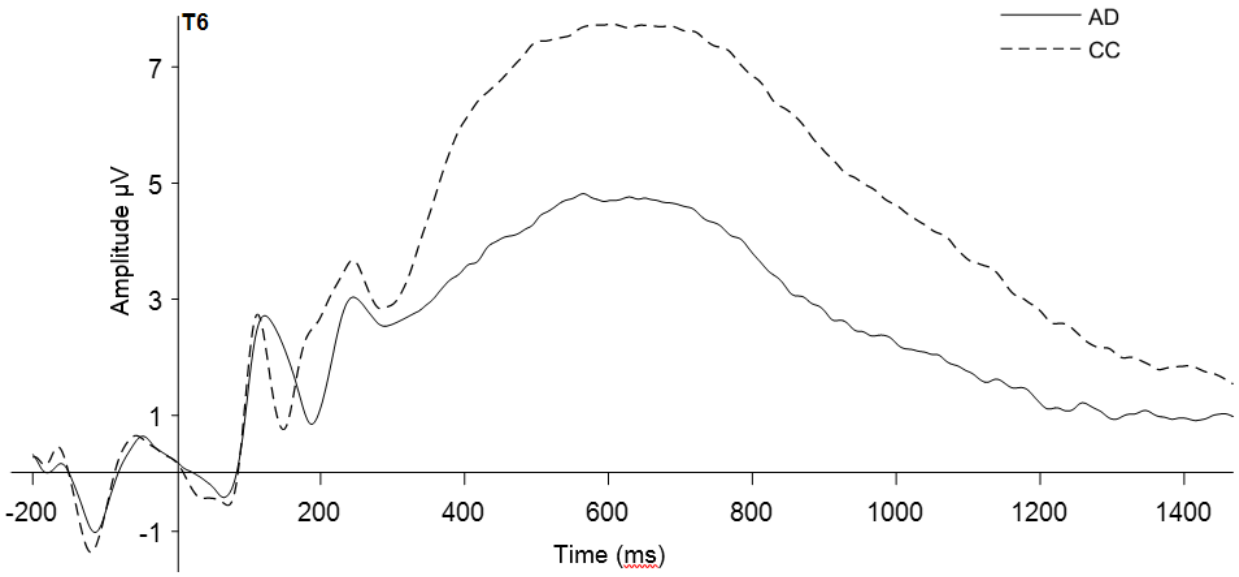

Figure 3-4. Grand Average EEG Waveforms: Emotion Judgement Task (Electrode T6). Y-axis = mean amplitude. X-axis = time from stimulus onset. Note the negative going deflection (N170) in both groups around approximately 200 ms. N170 amplitude, as measured between 110-180 ms (CC) and 130-200 ms (AD), did not significantly differ between groups. AD = alcohol dependent group. CC = community control group.

CHAPTER 4
DISCUSSION

The current study was designed to contribute to a growing literature addressing alcohol-related neurobehavioral concomitants of emotional facial expression (EFE) processing. More specifically, behavioral and neurophysiological measures were collected from alcohol dependent treatment seekers (AD) and non-alcoholic community controls (CC) during emotional and non-emotional task conditions. This investigation focused on group comparisons and attempted to: 1) replicate previous observations of alcohol-related EFE processing deficits and, if observed, 2) determine whether atypical neurobehavioral measures were specific to the processing of emotionally-laden content or generalizable to the evaluation of other facial attributes, 3) identify if atypical processing was specific to negatively-valenced emotions or to any one particular emotion, and 4) ascertain if EFE identification difficulties were associated with the extent of interpersonal problems.

Behavioral investigation of emotion processing with statistical analyses modeled to address a relatively small sample size yielded a significant difference between groups. More specifically, the assessment of emotion judgement task performance with a two (group: AD, CC) by three (emotion: happy, angry, sad) by two (morph: 65%, 95%) GLMM revealed less accurate emotion identification among ADs. These findings point to a subtle, but observable, alcohol-related behavioral deficiency that was generalizable across the positively- and negatively- valenced emotions examined in the current study. ERP findings paralleled behavioral outcomes, with ADs exhibiting attenuated P3 amplitudes across all emotions, regardless of valence, emotion-type, or EFE intensity. Importantly, the absence of group differences in behavioral and neurophysiological

measures for the sex judgement task suggested that alcohol-related neurobehavioral compromise was not generalizable to the explicit analysis of other facial attributes (i.e. masculine / feminine) and was, instead, specific to the analysis of emotionally-laden information.

Some studies have also revealed equivalent behavioral outcomes using the emotions assessed in the current investigation and presenting them at similar intensities (Philippot et al., 1999; Kornreich et al., 2003, 2001b). More specifically, alcoholics have previously exhibited less accurate EFE identification across happy, angry, and sad facial expressions. The study of anger and happiness, without sadness, has also yielded similar valence-related findings (Maurage et al., 2007a; Kornreich et al., 2001a). Furthermore, some of these investigations have extended the alcohol-related behavioral deficit to include additional emotions, such as disgust (e.g., Kornreich et al., 2001b, 2001a). Taken together, these findings, along with the current study's outcomes, might reinforce the hypothesis that the behavioral deficit is not valence-specific.

The current study's electrophysiological findings appear to implicate later processing stages in these behavioral deficiencies. Investigation revealed typical N170 characteristics among ADs, but attenuated P3 amplitude in response to all EFE stimuli. Among the very few electrophysiological investigations of explicit EFE processing in recently abstinent alcoholics, the neurobehavioral outcomes of one study correspond particularly well with the ones observed here. In this study, Maurage and colleagues (2008b) observed alcohol related behavioral deficits and altered P3 activity that was specific to emotion judgement and generalizable across happy, angry, and sad expressions. Investigation specifically revealed alcohol-related reaction time delays as

well as attenuated P3 amplitudes in response to sad EFEs and delayed latencies in response to happy and angry EFEs. The investigators' assessment of earlier ERP components did not implicate the N170 as a specific contributor to the emotion recognition deficit exhibited by ADs. Although the exact nature of behavioral compromise and P3 alterations differ somewhat from the current study's outcomes, the general pattern of results across our investigations seems to suggest alcohol-related emotion identification difficulties that generalize to positively- and negatively- valenced emotions and to implicate later processing stages in these behavioral deficiencies.

Investigation with other paradigms (e.g., oddball paradigm, multimodal visual conditions) has yielded comparable findings, providing evidence of EFE identification difficulties that are accompanied by atypical P3 elicitation, in the absence of N170 component alterations (Maurage et al., 2008d, 2008c). Although these higher-order perceptual processes are occasionally implicated (e.g., Maurage et al., 2007b), atypical activity at decisional processing stages appears to be more consistently observed. Importantly, visual inspection of the grand average waveforms in the current study guided N170 measurement in group-specific epochs. Although amplitude did not differ between groups and results concerning latency were generally consistent within groups, circumstances did not permit a direct assessment of group effects on N170 latency. While conclusions cannot be made as to whether N170 latency significantly differed between ADs and CCs, grand average waveforms suggested that between-group variability in N170 latency existed for both the emotion judgement and sex judgement tasks (hence N170 measurement in group-specific epochs for both tasks). Thus, if this study had permitted a direct comparison of N170 latency between groups, alcohol-

related delays may have been observed for general face processing, as opposed to EFE processing specifically. Still, visual examination of the data only permits speculation. Therefore, further investigation is needed to characterize N170 latency in ADs, relative to CCs, under emotional and non-emotional facial expression processing conditions.

Interestingly, some investigations have revealed an emotion processing deficit that is specific to or more pronounced for negatively-valanced emotions; Findings have been noted for both behavioral (e.g., Carmona-Perera et al., 2014; Frigerio et al., 2002) and neurophysiological (e.g., Maurage et al., 2008d, 2008c) measures. Furthermore, a subset of these studies have suggested atypical EFE processing that is specific to a single negatively-valenced emotion (e.g., Frigerio et al., 2002; Maurage et al., 2008c; Townshend & Duka, 2003). Although analyses conducted in the current study failed to reveal neurobehavioral impairment specific to any single emotion, the estimated differences between group means for accuracy and P3 amplitude were most produced for anger stimuli. Differences were particularly marked for moderate intensity presentations of anger. Our findings might point to a general neurobehavioral deficiency in emotion processing that exists for multiple expressions, but is more robust for certain emotions. Furthermore, these compromised functions might be most pronounced when the emotional expression is displayed at a lower, but decipherable, intensity. Indeed, previous research has suggested that abstinent alcoholics require greater emotional intensity in facial expressions for accurate identification (Frigerio et al., 2002). Therefore, intensity seems to play a role in the magnitude of observable impairment. In fact, many of the investigations that have observed an alcohol-related deficit for

negatively-valence emotions but preserved identification of positively-valenced emotions have used face stimuli depicting maximum intensity emotional expressions (e.g., Carmona-Perera et al., 2014; Frigerio et al., 2002; Kornreich et al., 2013). If the emotion processing deficit is more pronounced for certain emotions, and in particular, negatively-valenced emotions such as anger, observable impairment at maximum intensity presentations might only persist for these emotions. Importantly, the current report is not the first to propose the enhanced deficit for anger processing. Maurage and colleagues have previously emphasized the role of anger in alcohol-related emotion processing impairments (Maurage et al., 2008d, 2008c) and a recent meta-analysis suggested that group-related (AD vs CC) effects might be most pronounced for anger (although disgust was also noted; Bora & Zorlu, 2017). Given that the magnitude of observable impairment appears to vary by emotion and intensity of presentation also seems to impact reported findings, a more dynamic approach to understanding alcohol-related emotion processing deficits might be warranted. For some emotions, the deficit might emerge more readily, whereas other emotions may only reveal alcohol-related compromise under specific conditions (e.g., lower intensity expressions, more demanding tasks, etc.). Rather than identifying discrete deficits that either do or do not definitively exist, emotion processing alterations among alcoholics might be better understood if approached with respect to the likelihood that an emotion might reveal impairment. In other words, the deficit for a given emotion might belong on a continuum, rather than in a category.

Characterizing emotion processing in alcoholism has important implications for treatment and recovery outcomes. Facial expression is a chief component of non-verbal

affective communication (Eimer & Holmes, 2002). Deficient processing of emotional facial cues, and subsequent misidentification of emotions and intentions, might lead to negative social outcomes and interpersonal conflict (Uekermann & Daum, 2008). Interpersonal functioning has long been known to play a crucial role in recovery and maintenance of abstinence (Marlatt, 1996), and more recent research has demonstrated an association between poorer EFE processing and increased likelihood of treatment drop-out (Foisy et al., 2007a). Although limited evidence exists, a direct association between poorer emotion recognition and interpersonal problems has also been reported by two investigative teams (Kornreich et al., 2002; Maurage et al., 2009). Given the suggested import of EFE processing and interpersonal functioning in treatment outcomes, examining the relationship between the two might help provide a clearer understanding of emotion identification difficulties in recently abstinent alcoholics and better inform treatment efforts.

As expected, the current investigation revealed higher levels of interpersonal difficulty among ADs, relative to CCs, in all interpersonal domains assessed. Of greater interest, we observed a relationship between EFE identification and interpersonal functioning that showed group and emotion specificity. In particular, significant relationships were only observed among alcohol dependent participants and for angry facial expressions; Greater overall interpersonal difficulty was associated with less accurate identification of anger. Detailed characterization of this relationship further suggested that it might be attributable to certain interpersonal domains. Of the eight IIP-64 subscales, three exclusively shared a relationship with accuracy for anger, including the “intrusive/needy”, “nonassertive”, and “overly-accommodating” subscales. Again,

higher scores indicated greater difficulty in these interpersonal domains and were associated with less accurate identification of anger among ADs. Subscales can be organized along two dimensions, affiliation and dominance. Interestingly, the three scales for which this relationship emerged fall within the affiliation dimension, with the "intrusive/needy" scale reflecting friendly dominance and the "nonassertive", and "overly-accommodating" scales reflecting friendly submissiveness. These subscales speak to interpersonal problems that arise from a lack of self-confidence, difficulty managing social opposition, vulnerability to exploitation, and poor boundaries with others. Furthermore, difficulties in the 'overly accommodating' domain are specifically suggested to reflect a loathing to express and feel anger. Perhaps these traits hinder alcoholics' ability to identify anger in others. In contrast, difficulty identifying anger might promote uncertainty in the face of social opposition and exacerbate inappropriate responses to social cues. Although these data do not speak to causality, the relationships between these interpersonal domains and anger identification suggests that treatment efforts specifically aimed at ameliorating interpersonal problems within the affiliative dimension might also facilitate recovery of anger processing.

Although this is not the first study to reveal a relationship between emotion processing and interpersonal functioning among recovering alcoholics, it is, to our knowledge, the first to investigate this relationship with respect to EFE identification accuracy and emotion type. Maurage and colleagues (2009) have touched on emotion-specific associations in a previous study. However, their investigation concerned Likert scale ratings of emotional intensity for multiple emotionally-laden stimuli, including facial expressions, body postures, voices, and short stories. Accordingly, correlational

analyses were conducted for emotional intensity ratings collapsed across all stimulus types. Nonetheless, their findings suggested a positive relationship between interpersonal problems and intensity ratings among ADs that specifically involved the anger scale. Although methodological differences limit direct comparison with the current study, the assessment of anger appears to share a distinct relationship with interpersonal difficulties.

Taken together, the processing of anger might stand somewhat apart from other emotions. In the current investigation, atypical neural activity and misinterpretation of EFEs appeared to be more pronounced for anger, and poorer identification of angry expressions was associated with greater interpersonal difficulty. Although the alcohol-related emotion processing deficit was more robust for, but not specific to, anger, the relationship it shared with interpersonal problems was. Given the previously noted role of emotion processing and interpersonal functioning in disease progression and treatment outcomes, the role of anger in recovery from alcohol use disorders merits further consideration.

Importantly, the alcohol-related behavioral deficit observed in the current investigation was subtle. However, this subtlety might be explained by the implementation of a two-choice paradigm and investigation in a controlled laboratory setting. Emotion identification deficits might be more pronounced in real-world scenarios or with more complex task demands. However, previous studies have revealed a greater degree of behavioral impairment using similar methodological paradigms. One possible explanation for this discrepancy is variability in participant criteria for study participation. In an effort to address effects directly related to alcohol, the current

investigation enforced relatively conservative inclusionary/exclusionary criteria concerning comorbid mental / physical health conditions and current medication use. For example, a number of other investigations have recruited alcohol dependent samples without explicit exclusion for Hepatitis C, HIV, or ongoing benzodiazepine use (e.g., Philippot et al., 1999; Maurage et al., 2008b). Some studies have also failed to detail exclusion on the basis of comorbid psychiatric disorders (e.g., Kornreich et al., 2002). Serious physical health ailments have the potential to influence neurobehavioral function (Heaton et al., 2004; Perry et al., 2008) and comorbid psychiatric conditions, such as major depressive disorder and social phobias, are shown to affect EFE processing (Joormann & Gotlib, 2006). Therefore, inclusion of participants with these characteristics might yield a more pronounced deficit. Our investigation suggests atypical emotion processing even when these factors are carefully controlled for, although, behavioral presentation of the deficit might be somewhat less pronounced.

Interestingly, our investigation of behavioral efficiency did not reveal significant group differences for any task. This pattern might be explained by the observation that reaction times were slightly, albeit not significantly, faster among ADs relative to CCs. Given that accuracy among ADs was deficient but not severely impaired, a subtle tradeoff could have led to similar efficiency scores between groups. In other words, slightly faster responding at the cost of less accurate performance and in the absence of severe impairment, may have occluded a significant group difference in behavioral efficiency. To our knowledge, this is the first study of EFE processing in alcoholics to assess this measure. Therefore, additional investigation of behavioral efficiency

measures, particularly in larger sample sizes, will help to determine if a performance tradeoff exists for EFE processing.

Limitations

Limitations for the current study should be noted. Investigation was limited to alcohol dependent inpatient treatment seekers without significant psychiatric comorbidities or serious physical health ailments. Although this facilitated the formulation of conclusions directly pertaining to alcohol's deleterious effects, these findings might not generalize to populations with more complex diagnoses. Other investigations have begun to characterize emotion processing in alcoholics with dual diagnoses (e.g., Steinmetz & Federspiel, 2012) and additional research is needed among sub-populations presenting with and without comorbidities to determine whether or not various diagnoses modulate emotion processing deficits. Furthermore, the current study's sample size was relatively small and behavioral analyses had to accommodate for this issue in light of our complex design. Investigation with larger samples is necessary to confirm the findings reported here. Ongoing participant recruitment in our laboratory will allow us to address these issues and determine whether this pattern of results persists with an increased sample size.

Relatedly, the current study did not permit an investigation of sex main effects or interactions. Although we controlled for participant sex, sample characteristics restricted a meaningful analysis of its direct effect on alcohol-related outcomes. Almost all of the previously published studies reviewed in this document (Introduction) appear to have had similar constraints (but see Frigerio et al., 2002 and Fein et al., 2010), as alcohol dependent women are less frequently recruited than men. Given that sex has the potential to modulate emotion processing in healthy populations (see Hamann & Canli,

2004 for a review) and influence alcohol-related neurobehavioral compromise in various cognitive domains (see Nixon et al., 2014 for a review), future studies are encouraged to systematically investigate this factor when circumstances permit. Importantly, ongoing investigations in our laboratory are currently being conducted to address this understudied area.

As noted previously, the assessment of emotion processing with a two-choice paradigm may have reduced our ability to reveal the full extent of impairment in this otherwise healthy alcohol dependent sample. The tasks used in the current study were designed to accommodate electrophysiological assessment and limit potential complications during recording (e.g., excessive movement). Emotion judgement in realistic environments requires interpretation from a multitude of possible choices. Therefore, impairment might be more pronounced under real-world circumstances. Additional investigation of similar alcohol dependent populations in more naturalistic settings and with more complex tasks are warranted to characterize the full extent of emotion processing deficits.

In an effort to avoid participant fatigue, assessment of emotional facial expression identification was restricted to three emotions. Neurobehavioral assessment of emotion processing with tasks that incorporate additional emotions will provide further clarification regarding valence- and emotion-specific outcomes. The investigation of disgust might be particularly informative. Similar to anger, disgust has been proposed as one of the emotions for which alcohol-related compromise might be more pronounced. Future studies might also benefit from assessing the relationship between interpersonal problems and performance measures for this emotion. Finally,

electrophysiological assessment was limited to two ERP components. The examination of other ERP components reflecting different psychological processes will provide additional insight to the processing stages that contribute to emotion processing difficulties in abstinent alcoholics.

Conclusions

The current study demonstrated atypical emotional facial expression processing in alcohol dependent treatment seekers. Findings indicate subtle behavioral deficiencies and electrophysiological abnormalities that are specific to the evaluation of emotionally-laden content, generalize to positively- and negatively- valanced emotions, and implicate decisional processing stages in compromised emotion identification. These data also point to the enhanced role of anger in neurobehavioral compromise and in the relationship between emotion identification difficulties and interpersonal problems.

This investigation addresses a relatively understudied topic with significant potential to foster a more comprehensive understanding of alcohol use disorders. Given the dynamic interplay of emotion processing, interpersonal functioning, and treatment outcomes, findings have important and clinically-relevant implications. As the literature addressing this topic continues to grow, a clearer understanding of the deficit will emerge. Further investigation is needed to identify the emotions for which alcohol-related compromise is most pronounced and to better understand the relationship between various emotions and specific domains of interpersonal difficulty. Although alcohol-related compromise of emotion processing is far from being fully characterized, recent investigational efforts are elucidating the neurobehavioral and psychosocial components involved. These efforts, together with prospective studies, will advance our understanding of alcohol's deleterious effects and might ultimately provide a foundation

for the development of complementary therapies aimed at enhancing effective treatment and long-term recovery.

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BIOGRAPHICAL SKETCH

Lauren A. Hoffman was born in Los Angeles, CA. She graduated from Reseda High School in 2007 and earned her Bachelor of Arts in psychology from San Diego State University in the spring of 2011. Later that year, Lauren entered the Behavioral and Cognitive Neuroscience doctoral program within the University of Florida's Psychology Department and joined the Neurocognitive Laboratory under the mentorship of Dr. Sara Jo Nixon. Within this program, she was awarded a Master of Science degree in 2013 after successfully defending her master's thesis, which concerned sex differences in alcohol's acute cognitive effects. For her doctoral research, Lauren was granted the opportunity to pursue her longstanding interest in addiction psychology.

Following receipt of her Doctor of Philosophy degree, Lauren will continue to pursue a career as an addictions researcher. She intends to refine her investigational skills and further develop her interests in substance-use treatment by supplementing her neuroscience background with postdoctoral training in recovery-focused research. Ultimately, Lauren intends to conduct independent research that addresses treatment efficacy and methods of recovery aimed at reducing the risk of relapse.