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Neural and Behavioral Associations of Drinking and Empathic Processing

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DISSERTATION

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Abstract

Alcohol Use Disorder (AUD) is a major health problem, yet most individuals with AUD do not perceive a need for formal treatment and do not receive treatment. The lack of treatment seeking among individuals with AUD may suggest a lack of self-awareness and insight into the seriousness of AUD related problems. Moreover, individuals who have lost or are at risk of losing major relationships are especially likely to perceive the need for help. Thus, it may be the case that awareness of the influence of one's drinking on social relationships and the feelings of others (i.e., empathy) could improve treatment seeking among individuals with AUD. Given recent research, it is hypothesized that empathic processing (EP) is impaired among individuals with AUD and this impairment may explain continued heavy drinking despite disruptions in social relationships. Further, scant research to date examines alcohol-related neural atrophy in EP-related networks, which may explain deficits in EP among individuals with AUD. The current study examined the association between structural correlates of self-reported EP and heavy drinking among non-treatment seeking heavy drinkers with AUD ($N = 136$). Results showed scores on the Interpersonal Reactivity Index (IRI) Perspective Taking (PT) scale were inversely associated with temporoparietal and frontotemporal gray matter volume.

An interaction between IRI PT and sex was associated with alcohol craving, such that higher PT scores were associated with less craving for men, only. IRI Empathic Concern (EC) was related to fewer percent heavy drinking days for men and women. This replicated previous research finding sex differences on EP within an AUD sample (Robinson et al., 2018). The results may inform future research and suggest that sampling with regard to sex must be controlled and other brain-based phenotypes, particularly those that independently examine the functional correlates of effortful and more-automatic EP, should be investigated.

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Introduction

Globally, the heavy use of alcohol and alcohol use disorder (AUD) are among the leading causes of mortality and negative health outcomes (Grant et al., 2015; World Health Organization, 2011). Lifetime prevalence rates of AUD are estimated to be between 12 and 29% (Ross, 1995; Hasin et al., 2007; Grant et al., 2015). Moreover, approximately 80% of individuals with AUD do not perceive a need for formal treatment (Hedden & Gfroerer, 2011; Oleski et al., 2010; SAMHSA, 2013). While approximately 70% of individuals with AUD are expected to reduce their drinking without formal or informal treatment (de Bruijn et al., 2006; Dawson et al., 2006; Witkiewitz et al., 2011; Dearing et al., 2013), it remains unclear why some with AUD reduce their drinking without formal help, whereas just under a third of individuals with AUD continue to drink heavily despite the impact of drinking-related problems on family, friends, and extended social network members. One potential explanation may be the individual's ability to meaningfully internalize the experiences of others (i.e., empathy). It is hypothesized that lack of change in AUD may be at least partially explained by misperception of the harm caused by drinking consequences to others or an inability to emotionally comprehend the extent of that harm. It is the aim of the present study to investigate the neural and behavioral correlates of empathic processing (EP), drinking behavior, and perceptions of drinking consequences among heavy drinkers who are not treatment seeking.

1. Intersection of Social Factors, Empathic Processing, and AUD

It is argued that making goal-directed changes in addiction first requires the insight and self-awareness of the problem itself (Goldstein et al., 2009); however, such awareness rarely occurs in isolation of others. In AUD, insight into the consequences of an individual's drinking and treatment seeking may be contingent upon the ability to appropriately recognize and appreciate the social damages caused by drinking behavior (Hedden & Gfroerer, 2011). Pro-social influences, including marriage and supportive others, are correlates of drinking improvement (Havassy et al., 1991; McCrady, 2004, Tucker et al., 2004), and lacking social support is predictive of relapse (Witkiewitz & Marlatt, 2004). Psychosocial problems, especially within interpersonal relationships, have also predicted help seeking among individuals with AUD (Tucker et al., 1995).

It makes sense that recognition of problems in interpersonal relationships caused by heavy drinking could help individuals make reductions in their drinking. Empathic processing (EP), defined as the full host of neuropsychological abilities allowing a person to infer the mental and emotional states of others, may serve as a facilitating factor in recognizing such problems. Alternatively, impaired EP via the neurotoxic effects of alcohol/substance use may explain the persistence of socially-damaging behaviors in addiction. Prior research, among individuals in treatment, supports the proposed associations between EP and drinking behaviors, and has also investigated potential neural correlates of EP among individuals with alcohol dependence. Yet, little is known about the neural correlates of EP and drinking among individuals who have AUD and are not seeking treatment. The present work aims to address this gap by characterizing the

baseline neural and behavioral relationships between self-reported EP and drinking in a large sample of non-treatment seeking individuals with AUD.

1.1. The Sub-Abilities of EP and Related Networks

Empathy has previously been defined by De Vignemont & Singer (2006), who provided a comprehensive set of criteria: (i) one is in an affective state; (ii) this state is isomorphic (of different origin but sharing the same expression) to another person's affective state; (iii) this state is elicited by the observation or imagination of another person's affective state; (iv) one knows that the other person is the source of their own affective state (De Vignemont & Singer, 2006; Singer & Lamm, 2009; Walter, 2012). The work by Singer and colleagues indicates that a number of neural processes and abilities are involved in empathy including perspective taking, emotion contagion, and pain empathy.

Because of the large number of sub-constructs comprising empathy itself, the current research proposed the term "empathic processing" (EP) above, which is operationalized as the combination of neural processes and psychological abilities that allow for a representation of the other's experiences and intentions within oneself. What we call EP refers to the full host of abilities (e.g., perspective taking, emotion contagion, pain empathy, etc.) in representing the experiences of others and involves a variety of neural substrates. In order to investigate the neurological associations between drinking and EP, it is necessary to isolate the regions relating to both constructs.

1.2. Neuroimaging Targets for Empathic Processing Networks

Several reviews and meta-analyses have provided evidence for potential neural substrates of EP. This body of literature points to bottom-up, stimulus driven neural mechanisms that allow for the automatic contagion from another person to the self (i.e., mirroring) of visceral and affective experiences (i.e., interoception). For example, reviews and meta-analyses have provided support for the role of the insula and anterior cingulate cortex (ACC) in interoceptive mirroring (Craig, 2008; Keysers & Gazzola, 2006; Fabbri-Destro & Rizzolatti, 2008; Singer & Lamm, 2009; Decety & Lamm 2009; Lamm, Decety, & Singer, 2011). Therefore, we refer to these regions involved in some aspects of bottom-up driven EP as the "*interoceptive mirroring network,*" our original term for what Chiavarino & colleagues (2012) describe as a mirror neuron system of bottom-up mechanisms supporting EP.

The insula and ACC are typically activated while mirroring salient bodily states and highly visceral experiences (e.g., pain or disgust; Wicker et al., 2003; Lamm, Decety, & Singer, 2011). Activity in this network correlates with self-reported EP (Jabbi et al., 2007; Pfeifer et al., 2008) and accuracy when imitating facial expressions (Braadbaart et al., 2014), pain faces (Saarela et al., 2007), and viewing body parts in painful positions (Jackson et al., 2005; 2006; Cheng et al., 2007). These same regions have been linked to exacerbating addiction and reward circuitry and may contribute to craving-related experiences (Bechara, 2005; Naqvi & Bechara, 2009; 2010), which in turn may bias individuals with AUD away from intra- and inter-personal responsibilities which would necessitate drinking reduction and push them toward further drinking instead (Goldstein et al., 2009).

A distinct but conceptually-related system of regions called the "*representational mentalizing network*" also works to represent other's experiences and actions typically through facial or bodily non-verbal cues (Chiavarino et al., 2012). This network consists of a fronto-parietal system of mirror-functioning regions that represent short-term actions and experiences (Carr et al., 2003; Dinstein et al., 2007; Van Overwalle & Baetens, 2009; Shamay-Tsoory et al., 2011). The network includes areas such as the inferior frontal gyrus including the pars opercularis and pars triangularis sub-regions (IFG; Shamay-Tsoory et al., 2009; Saarela et al., 2007; Grosbras et al., 2012), inferior parietal lobe (IPL; Uddin et al., 2006; Preston & Newport, 2008; Cheng et al., 2009), temporoparietal junction (TPJ; Santiesteban et al., 2012), and superior temporal sulci/gyri (STS/STG; Carr et al., 2003; Leslie et al., 2004; Grosbras et al., 2012). Gray matter volume in the right IPL and right pars opercularis (IFG) correlates with self-reported EP (Cheng et al., 2009), and IPL activity has been associated with self-other distinction (Farrer & Frith, 2002; Uddin et al., 2006; Preston & Newport, 2008; Hetu et al., 2012), and even distinguishing human from artificial limbs in pain (Jackson et al., 2005). The STS is implicated in facial imitation (Carr et al., 2003) and imitation of hands and faces (Leslie et al., 2004) as a mirroring system region (Gallese, 2003; Van Overwalle & Baetens, 2009) and the IFG is implicated in emotion contagion (Shamay-Tsoory et al., 2009; 2011; Van Overwalle, 2009), mirroring (Grosbras et al., 2012), and shows activation correlating with pain observations and self-reported empathy (Saarela et al., 2007).

Other "top-down" or self-driven regions may work together to modify the aforementioned, stimulus-driven inputs (Cheng et al., 2007; Singer & Lamm, 2009). Chiavarino and colleagues (2012) argue that the representational system feeds into the

"conceptual mentalizing network" which integrates information from the representational system into more thorough understandings about others' narratives, beliefs, and enduring characteristics. The conceptual and representational networks share overlapping circuits localized around the medial prefrontal cortex (mPFC; Shamay-Tsoory, 2005; 2009; 2011) and TPJ (Saxe & Wexler, 2005; Van Overwalle & Baetens, 2009), which are often linked to EP during narrative-based tasks (Saxe & Wexler, 2005). The TPJ, posterior cingulate (PCC), and mPFC are each implicated in this top-down EP system (Amodio & Frith, 2006; Van Overwalle, 2009), which shows activity during a variety of EP-related activities. This includes suppressing the self-perspective in favor of another's (Ruby & Decety, 2001; 2003) and modulating pain empathy for others (Jackson et al., 2006; Cheng et al., 2007); in addition lesions to the left TPJ and vmPFC are associated with mentalizing deficits (Samson et al., 2004; Shamay-Tsoory et al., 2005). Regions such as the mPFC, PCC, and IFG show alcohol-related changes both structurally and functionally across studies (Grusser et al., 2004; Sinha et al., 2007; Le Berre et al., 2014), suggesting both the conceptual and representational systems may be affected by alcohol use as discussed below. The regions and networks referenced here and shown in Figure 1, are primarily the set most relevant to the discussion of EP and AUD.

A recent meta-analysis of 26 existing meta-analyses in the empathy literature spanning 3972 neuroimaging studies and 22,712 participants, derived a comprehensive list of 36 regions involved in the social brain connectome (Alcala-Lopez et al., 2017). The conclusions of this paper largely concur with the model presented here in that automatic (mirroring) vs. more effortful (self-driven) neural substrates seem to be grouped into four hierarchical networks in their model. A lower "visual sensory" network

comprised of the fusiform gyrus, occipital MT/V5, and pSTS was found in their clustering analysis driven predominantly by studies of social brain regions at rest (rather than during tasks). A second system made up of subcortical limbic and "old cortex" regions was found consisting of the bilateral amygdala (AM), hippocampus (HC), nucleus accumbens (Nacc), rostral anterior cingulate cortex (rACC) and vmPFC. What they label an "intermediate network" also consists of the anterior mid-cingulate cortex (aMCC), anterior insula (AI), IFG, cerebellum, and sensory motor regions. Their fourth network of "higher level" areas included the dmPFC, medial FP, PCC and precuneus, as well as bilateral TPJ, MTG, and temporal poles (TP).

Additionally, their hierarchical clustering analysis detected a greater trend for functional connectivity with other left-lateralized regions in the AM, HC, IFG, pSTS, and dmPFC. Functional correlates of the human mirror neuron system (Rizzolatti & Craighero, 2004; Rizzolatti, 2005) were observed primarily from analyzing regions of interest (ROIs) gathered from task-constrained studies rather than studies looking at resting state functional connectivity (Alcala-Lopez et al., 2017). This may be due to the multi-functionality of these networks as sensorimotor (Gallese et al., 1996; Gallese 2003), reward (Naqvi & Bechara, 2009), and emotion or pain-regulation circuits (Decety & Lamm, 2006; Cheng et al., 2007) in addition to serving those functions in a self-other understanding capacity. Therefore, empathy-eliciting tasks (as opposed to rest) may be required to gather data about the exact function of these networks together in empathic processing, however the current project used the coordinates of these ROIs in the subsequent neuroimaging analyses described below.

1.3. Neural Consequences of Alcohol Use and EP Deficits in AUD

Heavy alcohol use is associated with neurodegenerative effects throughout the brain and particularly in the frontal cortex (Ratti et al., 2002; Uekermann et al., 2005; Uekermann et al., 2007; Uekermann & Daum, 2008). The ACC, mPFC, nucleus accumbens, and insula in particular have been implicated in alcohol-cue and stress-induced craving, as well as drug seeking, which are hallmark characteristics of AUD (Contreras et al., 2007; Grusser et al., 2004; Jang et al., 2007; Le Berre et al., 2014; Naqvi & Bechara, 2009; Sinha & Li, 2007). Recent studies of individuals with AUD in treatment have identified general EP dysfunction (Bosco et al., 2013; Martinotti et al., 2009) and also deficits that are specific to emotional impairments, particularly for recognizing emotions in faces (Philippot et al., 1999; Maurage et al., 2009; 2011; Kornreich et al., 2013) and voices (Uekermann et al., 2005; Monnot et al., 2011). Alexithymia, or difficulty identifying emotions, is associated with deficits in self-other processing (Parker et al., 1993; Pedrosa Gil et al., 2009) and alexithymia is also correlated with heavy alcohol use (Uzun et al., 2003). Decreased recognition of emotional content, as well as a bias toward negative affect (often anger), are replicated findings across studies (Frigerio et al., 2002; Maurage et al., 2009; Dethier & Blairy, 2012).

Reorientation of the insula and ACC toward alcohol craving rather than self (and other)-awareness (Goldstein et al., 2009) might also impair EP abilities. Specifically, if the interoceptive network prioritizes addiction-related states that further drive addiction circuitry (Bechara, 2005; Naqvi & Bechara, 2010), then the interoceptive network may also fail to prioritize social and interoceptive cues such as the suffering of others (Singer

et al., 2004; Jackson et al., 2005; Cheng et al., 2007). Similarly, addiction-related deficits have been identified in the temporal (Franklin et al, 2002; Cservenka et al., 2014; Le Berre et al., 2014) and parietal (Le Berre et al., 2014; Thayer et al., 2016) regions of the representational system. As shown in Figure 2, a wide range of frontal, limbic, and temporoparietal areas have been implicated in alcohol-related dysfunction, which overlap with known EP networks.

One prior study has examined structural EP correlates in a drinking, at-risk drinking, and control sample (Schmidt et al., 2017) and found cortical thickness (CT) reduction of EP areas in patients with AUD compared to high risk drinking and non-high risk drinking controls. Furthermore, patients with AUD have shown decreased CT in the middle frontal gyri, insula, and precuneus relative to controls, which related to both cognitive and affective self-reported empathy (Schmidt et al., 2017). AUD patients also had lower scores on cognitive aspects of self-reported empathy (Bosco et al., 2013; Maurage et al., 2015; Schmidt et al., 2017). Because the Schmidt study involved cortical thickness measures, many of the affective correlates of EP that involve subcortical regions were not investigated.

It may be the case that individuals with severe AUD would show wide-ranging deficits on neurological correlates of EP, whereas those with less severe AUD whose heavy drinking has not necessitated formal treatment might have sparing in EP networks. Most of the previous work examining AUD and EP has been conducted with individuals already enrolled in treatment or treatment seekers (Pfefferbaum et al., 1992; Philippot et al., 1999; Grusser et al., 2004; Jang et al., 2007; Maurage et al., 2009; 2011; Kornreich et al., 2013; Le Berre et al., 2014), thus the present work aims to extend prior research by

examining the unique associations between self-reported EP and structural, neurological correlates of EP with drinking among non-treatment seeking individuals with AUD.

1.4. Structural EP Relationships with the Interpersonal Reactivity Index (IRI)

The Interpersonal Reactivity Index (IRI) is the most widely used measure of empathic processing (EP) ability (Chrysikou et al., 2016) that assesses EP across four factors, 2 affective: Empathic Concern (EC), Personal Distress (PD); and two cognitive: Perspective Taking (PT) and Fantasy Simulation (FS). In a sample of methadone patients, factor analysis was able to distinguish between the Perspective Taking and Empathic Concern dimensions while Personal Distress was more related to neuroticism (Alterman et al., 2003), suggesting a similar factor structure may be found for heavy alcohol users. Among recently detoxified individuals with AUD (compared to controls), Maurage and colleagues, (2011) found lower scores on the affective but not cognitive subscales of the IRI. On the contrary, a subsequent study found cognitive but not affective scores were reduced in a similar sample (Maurage et al., 2015).

More recent studies have found a complex series of relationships between structural correlates relating to EP and scores on the IRI. Studies involving some type of brain injury or neurodegeneration tend to show positive correlations between EP gray matter ROIs and IRI EC or PT (Shdo et al., 2017; Rushby et al., 2016; Rankin et al., 2006; Hooker et al., 2011). A few studies assume positive relationships with IRI EC in neurodegenerative samples (Shdo et al., 2017; Rankin et al., 2006); however, in healthy or community samples, gray matter volume may reflect a “less is more” property (Banissy et al., 2012, p. 2037) whereby efficiency in the brain allows for less gray matter to produce improved functioning overall due to improved cortical organization (Durston

& Casey, 2006). This may explain inverse relationships between IRI EC and anterior insula and left precuneus gray matter volume in 118 healthy individuals (Banissy et al., 2012) and inverse relationships between IRI PT and cortical thickness in the left IFG and other frontal gyri in 13 patients with AUD (Schmidt et al., 2017).

In these same studies however, there were also positive relationships between EP gray matter correlates and IRI scores such as IRI FS correlating positively with insular gray matter volume (Schmidt et al., 2017) and IRI PT scores correlating positively with left anterior cingulate gray matter (Banissy et al., 2012). Moreover, studies in healthy samples also show positive associations between gray matter volume in known EP regions and IRI factors. For example, Cheng and colleagues (2009) found that gray matter volume in the right IFG, right IPL, and right medial PFC correlated positively with IRI EC in healthy subjects. Attempting to replicate Banissy and colleagues (2012), Cheetham et al., (2014) found positive associations between insular volume and IRI FS scores while volume in two regions of the dmPFC inversely related to FS and showed no relationship with IRI PT. If using voxel-based morphometry, the complexities and uncertainties of these relationships between EP structural correlates and self-reported IRI scores necessitates examining these associations while controlling for age, sex, and intracranial volume, as per other studies (Banissy et al., 2012; Cheng et al., 2009; Cheetham et al., 2014; Schmidt et al., 2017).

In the current project, voxel-based morphometry (VBM) controlling for age, sex, and intracranial volume, as per other studies (Banissy et al., 2012; Cheng et al., 2009; Cheetham et al., 2014; Schmidt et al., 2017) was performed to associate gray matter (GM) the IRI factors (Aim 1). We also used source-based morphometry (SBM) to derive

independent components of correlated GM regions and associated those components with the IRI as well. Thereafter, we then used these GM associations with the IRI to predict drinking variables (Aim 2) in the regression models described below. Also, following studies investigating sex differences on EP (Cheng et al., 2009; Robinson et al., 2018), we investigated effects of the interaction of the IRI, GM, and sex on drinking variables as discussed in further detail below (Aim 3).

1.5. Possible Clinical Relevance and The Current Project

Understanding how deficits in EP manifest among individuals with AUD has important prevention and intervention implications. Help-seeking is related to greater social and relational problems (Tucker, 1995) and those who are widowed, separated, or divorced are more likely to seek treatment (Oleski et al., 2010; Hedden and Gfroer, 2011). Therefore, it may be beneficial to intervene with heavy drinkers by exercising their empathic processing skills, increase the relevancy of their drinking-related interpersonal problems, and possibly motivate change. Some studies have linked mindfulness-based compassion trainings, for example, with changes in social-connectedness, increases in positive affect (Robinson et al., 2017), and greater feelings of warmth for others and the self (Kok & Singer, 2017). Existing evidence shows positive changes both in how individuals feel generally (Klimecki et al., 2012; Kok & Singer, 2017), and how they feel about external stimuli (Hutcherson, Seppala, & Gross, 2008). Even a 1-day mindfulness training compared to memory training resulted in greater ratings of empathy for distressed others, increases in experienced positive affect, and evidence of neuroplastic changes, indicating that mindfulness effects on emotion

regulation and social connectedness may be recognizable at the neural level (Goldin et al., 2010; Klimecki et al., 2012).

Mindfulness interventions have also been successfully used to treat AUD as reported across a variety of studies (Witkiewitz et al., 2013; Garland et al., 2014). Therefore, it may be possible to motivate change via incorporating more mindful attention to the possible EP-related deficits indicative of heavy drinking. Before any EP-related interventions can ever be used to help treat AUD or any other use disorder, the demographic, behavioral, and neurological underpinnings of EP within heavy drinking require more in-depth examination. For example, previous research has found that EP specifically relates to less drinking in men but not women (Robinson et al., 2018) which might be meaningful for the application of certain mindfulness exercises acting on EP to treat AUD.

Therefore, the current study recruited a community sample of non-treatment seeking heavy drinkers to examine the psychosocial, behavioral, and neural mechanisms relating to EP and heavy drinking. The innovation rests in the unique research questions being asked and the novelty of gathering neuroimaging data in a community sample of heavy drinkers who are not treatment seeking. This is the first study to combine structural imaging correlates of EP and a well-validated assessment of empathy in a series of regression models including age and sex covariates to test the effects of EP and EP-related GM on drinking in a community sample.

We correlated structure in EP-related networks with self-reported EP in a sample of non-treatment seeking heavy drinkers in a model controlling for age and sex. We then used different versions of this modelto predict drinking variables. The over-arching aim

of the study was to characterize how neural correlates of self-reported EP and EP-related gray matter may be associated with heavy drinking, alcohol craving, and drinking consequences.

2. Methods

The current study is part of a larger longitudinal study to examine behavioral and neural mechanisms of change among non-treatment seeking heavy drinkers assessed at baseline and with follow-ups conducted at 3-, 9-, and 18-months post-baseline (R01AA023665). The focus of the current study was the baseline neural correlates of a self-report measure of EP, the Interpersonal Reactivity Index (IRI, Davis, 1980), alcohol consumption as measured by the Form 90 (Miller, 1996), drinking consequences as measured by the Short Inventory of Problems (SIP; Miller et al., 1995) and alcohol craving as measured by the PACS (Flannery et al., 1999) each assessed at baseline.

The Alcohol Use Disorder Identification Test (AUDIT; Saunders et al., 1993) was used to assess the extent of drinking behavior and determine participant eligibility, with the goal of recruiting heavy drinkers. Inclusion criteria included: (1) AUDIT scores of 9 or greater (males) and 8 or greater (females); (2) right-handed; and (3) between the ages of 22 and 55. Exclusion criteria included: (1) Seeking alcohol treatment or any form of help to reduce drinking (e.g., Alcoholics Anonymous meetings) currently or in the prior 10 years; (2) Prior traumatic brain injury or neurological diagnoses; (3) Met criteria for lifetime bipolar disorder or schizophrenia; (4) Met criteria for current substance use disorder not including nicotine or marijuana; (5) Tested positive for an illicit drug (other than marijuana) on the baseline urine screen; (6) Contraindications for MRI (e.g. ferrous metal in the body); (7) Female participants who were pregnant; (8) Estimated IQ < 80; (9) Unable to read or speak English fluently; or (10) History of severe alcohol withdrawal (e.g. seizures, tremors, DTs).

A sample size of N=136 with baseline data was analyzed for the proposed study. Power analyses were conducted to determine sample size using a bivariate standardized correlation coefficient r (r^2) = -0.41 (0.168) that was derived from Maurage and colleagues' (2011) correlation of total score on empathy using the Empathy Quotient (EQ; Baron-Cohen & Wheelwright, 2004) and the Inventory of Interpersonal Problems (IIP; Horowitz et al., 1988). Power analyses in G*Power (Faul et al., 2009) and an original power calculator in Excel indicated we would have 80% power to detect a significant association between EP and drinking consequences with an approximate sample of N=44. This calculation however, relies upon effects within more severe treatment-seeking drinkers (Maurage et al., 2011) rather than a community sample as was used in the current study. Because of this, effects may be smaller in the current sample requiring a larger sample size for adequate power.

2.1. Procedure

The baseline assessment was the focus of the current study. Participants completed a clinical assessment and neuroimaging, including both structural and functional magnetic resonance imaging (MRI); however, only structural data are of interest in the present analysis. Breathalyzer tests were conducted prior to all interviews. Participants with a BAC greater than 0.0 were rescheduled or were given snacks and water until their BAC was reduced to a safe level in accordance with NIAAA guidelines (BAC < .02 - .04 mg%). Participants arrived to the Mind Research Network (MRN), and completed the IRI as part of an initial assessment-focused visit. Scan visits typically

occurred on separate days beginning with structural scans, rest, and other functional scans as described below.

2.2. Measures

Primary Drinking-Related Variables. The *Form 90* (Miller, 1996) is an interview method for the reliable collection of calendar-based alcohol use data (Tonigan et al., 1997) and illicit drug use data, including information regarding treatment (including AA attendance), arrests, or hospitalizations. At baseline, drinking days up to 90 days prior to that visit are assessed for each subject. The Form 90 was used to derive estimates of the primary outcome variables: total SEC or total number of drinks, number of drinking days, percentage of drinking days, percentage of heavy drinking days, and number of drinks per drinking day.

Data from the Short Inventory of Problems (SIP; Miller et al., 1995; Forcehimes et al., 2007) was used to measure the consequences related to alcohol consumption. This measure was adapted from the Drinker Inventory of Consequences as a shorter, 15-item, self-report questionnaire (Miller et al., 1995). Previous research suggests the SIP is reliable and useful when assessing overall drinking-related consequences (Forcehimes et al., 2007). Cronbach's alpha for the SIP in the current dataset was α=0.92.

The Penn Alcohol Craving Scale (PACS; Flannery et al., 1999) was also used to estimate the subjective experience of craving for alcohol. This five-item self-report measure covers questions regarding the intensity, frequency, and ability to resist craving and has demonstrated strong psychometric properties in past treatment samples (Flannery

et al., 1999). In the current non-treatment seeking sample, the Cronbach's alpha was α=0.86.

Empathic Processing: Interpersonal Reactivity Index. This 28-item self-report questionnaire conceptualizes EP using a four-dimensional model: Perspective Taking, Empathic Concern, Personal Distress, and Fantasy Simulation. Perspective Taking measures cognitive perspective taking, while Empathic Concern is operationalized as highly related to emotional perspective taking (Davis, 1980). Fantasy Simulation (FS) refers to the ability to experience overlap with fictional characters and Personal Distress reflects the extent to which sharing in another's experience may result in aversive states for the participant. The Cronbach's alpha for the total IRI items in this sample was α=0.79. Cronbach's alpha for IRI EC was α=0.77, alpha for IRI PT was α=0.76, alpha for IRI FS was α=0.77, and alpha for IRI PD was α=0.75.

2.3. Neuroimaging Sessions and Preprocessing

For scanner-eligible individuals, participants were in the MRI scanner for 1.5 hours. All participants were instructed to abstain from drinking alcohol for at least 24 hours before the scanning session. Participants are also given an MRI screening form to measure potential contraindications and a urinalysis drug screen to detect illicit substances that may affect scanner data. Individuals with scanner contraindications or a positive urinalysis test were not scanned. All MRI scanning was conducted on a Siemens Trio TIM scanner equipped with a 32-channel radio-frequency coil using multiband sequences for volume collection. A T1 image for voxel based morphometry (VBM) analysis was collected using an MPRAGE pulse sequence collecting 224 slices in the

sagittal plane, 0.8x0.8x0.8 mm voxel resolution, TE = 2.01 ms, TR = 2400 ms, TI = 1000 ms.

The T1-weighted images derived from this project underwent standard preprocessing guidelines (Ashburner & Friston, 2000; Good et al., 2001) including normalization to a stereotactic space, segmentation into gray matter (GM) white matter (WM), and cerebrospinal fluid (CSF), and smoothing with a 10 mm^3 full width at half maximum (FWHM) Gaussian kernel with modulation as part of an automated preprocessing pipeline. First, images were normalized to the average 152 MNI T1 template provided by the Statistical Parametric Mapping package version 8 (SPM8). Normalization involves a two-step process by which the individual MR images are mapped to the template and then altered to minimize the squared differences between each image and the template (Ashburner & Friston, 2000; Mechelli et al., 2005). Images used were in 2 mm^3 voxel space using the Montreal Neurological Institute (MNI) 152 coordinate system. Using smaller millimeter cubic spaces helps to limit the effects of capturing "partial volume" of gray or white matter in a single voxel during the segmentation step (Ashburner & Friston, 2000).

In segmentation, the normalized images are separated into gray matter, white matter, or cerebrospinal fluid (CSF) partitions. This is done using *a priori* probability maps (i.e., Bayesian priors) which provide information about the loci of tissue types in healthy brains in a mixture model cluster analysis identifying those same tissue types in the present images by the intensity of each voxel (Mechelli et al., 2005). Following this, the GM, WM, and CSF images were smoothed using a 10 mm^3 FWHM smoothing kernel, as discussed above. Smoothing essentially blurs an image and reduces the overall

number of independent observations. Mathematically, each voxel in a given image is replaced with a weighted average of itself and its neighbors as defined by the size of the smoothing kernel (Brett et al., 2003). This makes the data per each voxel more Gaussian for parametric statistical tests to be conducted.

To correct for the changes in individual head shapes deformed after the spatial normalization step, it is necessary to undergo the modulation step, multiplying each voxel by the Jacobian determinant derived from normalization. In this way, the individual differences in GM/WM per subject are preserved before and after spatial normalization allowing for absolute GM/WM volume scores to be saved out per subject rather than the concentration of GM/WM relative to other tissue types (Good et al., 2001; Mechelli et al., 2005).

2.4. Analytic Strategy: Voxel-Based Morphometry (VBM)

The different factors of the IRI were entered into a regression model with age, sex, and intracranial volume as additional covariates, predicting gray matter voxel intensity in a whole-brain VBM analysis with Family-Wise Error (FWE) correction. This model was also tested separately by sex, given sex differences typically observed on the IRI and in gray matter (Cheng et al., 2009). The FWE correction used here involves the use of Random Field Theory (Brett et al., 2003) which takes into account the non-independence of spatially proximal voxels when conducting (and alpha-correcting for) a series of voxel-wise tests such as the VBM analyses described above. We also used the False Discovery Rate, or “FDR” correction for analyses at this stage but this did not have an effect on the results. The smoothness (spatial correlation) of a given image is first

estimated and the number of independent spatial units in the image or the "Euler Characteristic" is determined which essentially determines how the alpha level will be corrected. Each statistical test from the above regression models at each voxel was corrected using this procedure in SPM8.

2.5. Analytic Strategy: Source-Based Morphometry (SBM)

The above a priori approach was compared to a more data-driven approach using Source Based Morphometry (SBM; Xu et al., 2009; Kubera et al., 2014). SBM uses Independent Component Analysis (ICA; Bell & Senjowski, 1997; Makeig et al., 1997) to separate structural imaging data into a pre-specified number of spatially independent sources by accounting for the interrelationships between voxels and grouping them into natural yet independent components. An infomax algorithm was used to decompose the signal from the preprocessed GM volume images into maximally independent sources/components (ICs) (Bell & Senjowski, 1997; Makeig et al., 1997; Xu et al., 2009). These components are therefore made up of GM regions showing inter-correlations with each other but minimized correlations between the components to which they belong.

In SBM, GM data are converted into matrices whereby the rows represent subjects and the columns represent voxels. This is decomposed by ICA into two separate matrices: a "source matrix" representing the relationship between each voxel and each component derived; and a "mixing matrix" representing each subject per row and each IC per column. The values in the mixing matrix are loading coefficients that represent each subject's relationship (or "loading") to that average component across all subjects

(Grecucci et al., 2016; Xu et al., 2009; Luo et al., 2012). These scores for each subject were saved out for subsequent analyses.

ICA was conducted using 20 iterations in ICASSO across the whole brain and scaling voxels in the components by z score. Doing this allows a comparison between results of more theory- and more data-driven approaches in examining the relationship between EP and drinking variables in this community sample. As stated above, each participant's loading onto (or relationship with) each of the ICs derived here were saved out and added to the dataset to be used in the modeling procedures described below.

2.6. Regression Analyses

To our knowledge, few prior investigations have examined EP-associated gray matter in the brain, particularly among individuals with an AUD; only one study to date has examined relationships between cortical thickness and EP in an AUD sample (Schmidt et al, 2017). To further elucidate the role of EP-related ROIs in relationship to drinking behavior, we used the SBM independent components in a series of regression models to estimate drinking consumption, consequences, and craving alongside the IRI, age, sex, and interactions between the SBM components with sex and IRI factors with sex. Each IRI factor was tested in a separate regression with these same covariates. Therefore, we attempted to replicate Schmidt and colleagues' (2017) findings while taking into account the covariates that may affect relationships between drinking, brain regions, and empathic processing.

Aim 1 tested all of the SBM components that showed correlations with the IRI by controlling for age, sex, and total gray matter volume. The regressions for Aim 2 used this basic model to then test associations with drinking variables, consequences, and craving, while the interaction effects in those regression analyses tested Aim 3 by using interaction terms for the IRI*sex, and the SBM gray matter component*sex thereafter testing the simple slopes for significant interactions wherever appropriate.

Missing data were primarily on the neurological variables due to MRI scanner contraindications or exclusion due to preprocessing errors, therefore data were assumed to be missing at random. Out of the total sample of 136, n=114 were able to be scanned but 9 of those had preprocessing errors in their GM volume images and had to be removed, hence the models using only neurological variables use the imaging sample (n=105). Missing neuroimaging data was due to a variety of reasons including: missing MRI appointments and failing to reschedule, being too claustrophobic for the scanner or poor scanner behavior as indicated by notes, withdrawing from the study, having piercings or implants ultimately deemed unsafe for the scanner, and finishing the MRI visit after the final dataset for this analysis was compiled.

An additional participant was an outlier on total GM volume and was excluded, bringing the VBM sample down to n=104. Out of the 104 used for the VBM/SBM analyses, 6 participants in the sample were missing data on the Form 90 due to their data having not been entered or fully conflict-corrected, which essentially reduced the sample size for regression analyses investigating drinking consumption variables such as percentage of heavy drinking days down to n=98, while analyses of alcohol craving or drinking consequences still used the full 104 available.

2.7. Aims, Hypotheses, and Associated Models

1) Aim 1: Identify the structural gray matter (GM) correlates of EP in heavy drinkers at baseline.

Our hypothesis for aim 1 was that EP-related GM would be significantly negatively associated with IRI EC and IRI PT (Schmidt et al., 2017; Banissy et al., 2012); we did not have directional hypotheses for IRI FS or PD.

Whole-brain VBM methods were used to investigate the GM correlates of EP. A regression model including each IRI factor as predictors of GM with age, sex, and total intracranial volume (as well as total gray matter volume) as covariates was estimated (Cheng et al., 2009; Banissy et al., 2012) using GM volume per voxel in our modulated GM volume images, as the dependent variable. The method in VBM relies upon the assumption that the IRI factors directionally "predict" gray matter volume in a regression model controlling for other nuisance covariates (age, sex, total gray matter volume). To investigate aim 1 with greater flexibility, we saved out the loading coefficients from a whole-brain SBM analysis and tested each component's associations with the IRI dimensions. The most-associated SBM component with the IRI was used as the final model to test the aim 1 hypothesis. Comparing models involved comparing the R^2 (variance explained) for the dependent variable of interest—in this case of aim 1, this meant reporting variance explained in the IRI factors.

2) Aim 2: Examine the association between EP-related gray matter and alcohol consumption (primary outcome), as well as drinking-related consequences and craving for alcohol (secondary outcomes) at baseline.

Our hypothesis for aim 2 was that self-reported EP and EP-related gray matter (GM), together, would be inversely related to drinking, drinking consequences, and alcohol craving at baseline.

The inverse nature of the relationship between GM volume and substance use (Franklin et al., 2002; Naqvi & Bechara, 2009) or drinking (Kril et al., 1997; Xiao et al., 2015; Thayer et al., 2016) is well-documented. The precise nature of the relationship between IRI factors and drinking is a bit less clear. Recently detoxified individuals with AUD show deficits on IRI EC compared to controls, but no deficits in PT or FS (Maurage et al., 2011). In other studies, individuals with AUD have been found to have deficits on IRI PT scores, but none of the other IRI factors (Maurage et al., 2015). Therefore, we predicted that the SBM gray matter components and IRI factor scores would be inversely related to drinking at baseline. Regression models were assessed by examining the R^2 (variance explained) on drinking variables.

3) Aim 3: Assess the extent to which interactions between sex, the IRI, and EP-related GM might be associated with drinking variables, craving, and drinking consequences.

Nearly all studies investigating relationships between EP and gray matter volume control for age, sex, and either total gray matter volume or total ICV (Cheng et al., 2009; Banissy et al., 2012; Schmidt et al., 2017). Further, there is increasing evidence of sex differences on the construct of EP itself, structurally (Cheng et al., 2009; Mutschler et al., 2013), via self-report (Davis, 1980; Baron-Cohen & Wheelwright, 2004), and as EP relates to drinking (Robinson et al., 2018). Further, the relationship between IRI scores and GM volume seems to be moderated by age-related neurodegenerative disease such

that studies of stroke or Alzheimer's patients consistently show positive associations (Rankin et al., 2006; Hooker et al., 2011; Shdo et al., 2017) while healthy or drinking samples show mixed and often negative associations (Banissy et al., 2012; Schmidt et al., 2017). For these reasons, we performed an exploratory investigation of the interaction between the SBM gray matter components with sex and the IRI factors with sex as interaction terms in the regressions to predict drinking. All main effects were grand-mean centered. Our only hypothesis in regards to this aim was that simple slopes analyses of the interactions would show that associations between drinking, EP-related gray matter networks, and/or IRI factor scores would be stronger for men than women (Robinson et al., 2018).

3. Results

3.1. Preliminary Analyses

The sample (N=136) was predominantly male (n=76, 55.9 %), and predominantly white (n=84, 61.8%), with an average age of 33.9 (SD=9.6). The sample also consisted of a large sub-group who identified as Hispanic/Latino (n=65, 47.8 %). Over one third of the sample identified as non-Hispanic white (n=52, 38.2%), while under one quarter of the sample identified as both white and Hispanic/Latino (n=32, 23.5 %). Average score on IRI EC was 21.18 (SD=4.66), with a minimum score of 6 and maximum score of 28. The average score on IRI PT was 20.1 (SD=4.52), with a minimum score of 7 and maximum score of 28.

Several studies using the IRI use the "Saarbrücker Persönlichkeitsfragebogen" or "SPF," a revised and validated German version of the IRI (Paulus, 2006; Gizewski et al., 2013) that removes the reverse-coded items to avoid confusion. All analyses were conducted with both the IRI and SPF factors revealing no differences in this sample, therefore we report model results below using the full IRI. Mean score for the SPF EC items in this sample was 12.12 (SD=2.78), while mean score for the SPF PT items was 14.99 (SD=3.46). Interestingly, the current sample had lower average SPF EC and higher average SPF PT scores, as compared with the AUD sample recruited by Schmidt et al. (2017). The AUD sample in Schmidt consisted of only n=13 individuals who were predominantly males, whereas our AUD sample is considerably larger and more demographically-balanced.

Average number of drinks consumed in the 90 days leading up to baseline for the whole sample was 290.15 (SD= 284.47). Average percentage of heavy drinking days for

the full sample was 28.78% (SD=26.32%) and average drinking consequences was 9.79 (SD= 7.66), out of 15 possible consequences. Average number of drinks per drinking day for men was 6.77 (SD=4.73), while average number of drinks per drinking day for women in this sample was 5.55 (SD= 4.64). Average number of drinks per drinking day for the entire sample was 6.24 (SD= 4.21).

We performed six exploratory t-tests, alpha-corrected for multiple, unplanned comparisons, in order to explore the nature of the sex differences on the IRI and drinking outcomes (Robinson et al., 2018). Specifically, t-tests were performed between male and female scores on IRI EC, IRI PT, IRI FS, and IRI PD as well as Total SIP (drinking consequences), and Total SEC (total number of standard drinks consumed in the 90 days leading up to baseline) and evaluated using a Sidak-corrected alpha-level of α=0.008 for multiple comparisons. Although women scored higher on both IRI EC and IRI FS in this dataset there were no sex differences on IRI PT or IRI PD (see Table 2). There were also no sex-differences on total SEC (M_{males}=301.41, SD: 288.78; $M_{females}$=275.81, SD: 280.88; p=0.62) or drinking consequences (M_{males}=8.54, SD: 6.86; $M_{females}$=11.38, SD: 8.36; p=0.031; critical α_{sidak}=0.008). As is typically shown on the construct of EP (Davis, 1980; Robinson et al., 2018), women in this sample scored statistically higher on EP as measured by the IRI's EC factor compared to men (M_{males}=19.95, SD: 4.77; $M_{females}$=22.75, SD: 4.04; $p_{observed}$<0.001; critical α_{sidak}=0.008). See Table 2 for a full list of sex differences on the IRI and SPF dimensions as well as mean scores.

We also observed a significant correlation between sex and age (r = -0.21, p = 0.039), which resulted in collinearity between these covariates in our models. Although this is a modest relationship, age and sex are not typically correlated in healthy and

representative non heavy drinking samples. Therefore, the present parameters for age and sex in this sample may introduce bias, which can present modeling concerns (Wolf et al., 2013). There was also a large negative correlation between intracranial volume (ICV) and sex ($r = -0.85$, $p < 0.001$). Likewise, total gray matter volume was correlated with both age ($r = -0.39$, $p < 0.001$) and sex ($r = -0.27$, $p = 0.004$). The presence of any combination of more than two of these covariates, age, sex, and total ICV (or total gray matter volume), while allowable in the VBM analyses, presented model collinearity issues within the regression framework as discussed below. Having tested the model with each covariate alone, pairs of them together, and all covariates together, it was determined that these variables were the most likely cause of model collinearity issues suggesting relationships between these variables may also cause overlap in how they explain variance in the other GM, IRI, and drinking variables in the final models.

3.2. Aim 1 Results Based on Voxel Based Morphometry (VBM) Gray Matter Associations with the IRI

A series of multiple regression analyses were conducted in SPM 8 using the preprocessed and modulated GM volume images at each $2x2x2mm^3$ voxel throughout the whole brain as the dependent variable. Each factor of the IRI was used as the parameter of interest in the same design matrix while age, sex, and total gray matter volume, were used as covariates. We drew our type of statistical design from the methods of Banissy & colleagues (2012) who also used multiple regression with these same covariates.

We also tested total intracranial volume as a covariate but regardless, neither intracranial volume, nor total gray matter volume, ultimately had an effect on the IRI

results as confirmed via running the model with and without these covariates. Further, there were no differences in results for all IRI factors when excluding the age, sex, total gray matter volume, and other IRI covariates either. Two-tailed tests were used here, so the Family-Wise-Error (FWE) corrected p-value was also set to 0.025 for testing both tails (both the positive and negative associations between IRI factors and gray matter). We also re-tested results using an FDR correction; however, this had no effect on results or conclusions. Each IRI factor was also tested separately, controlling for age, sex, and both total gray matter volume or total intracranial volume in different design matrices. Because results were not different controlling for total gray matter volume or intracranial volume, we report results for intracranial volume for the VBM below.

Out of all the VBM regressions and sensitivity analyses conducted, the only significant covariates in predicting GM volume were age and total ICV. Higher age significantly predicted less GM volume in voxels located primarily in the frontal cortex (see Table 3 for list of peak voxels as well as Figure 3 for visualizations). Greater total ICV also significantly predicted higher gray matter volume across the whole brain (see Figure 4). None of the IRI factors significantly predicted the voxel-wise volume of gray matter examined in the VBM.

3.3. Aim 1 Results Based on Source Based Morphometry (SBM) Gray Matter Associations with the IRI

Out of the 20 whole-brain gray matter components estimated, only the fifth gray matter component (see Figure 5) showed a significant correlation with IRI PT (see Table 4) which prompted testing associations between this component and the IRI while

controlling for age, sex, and total gray matter volume. IRI PT was significantly inversely associated with this SBM component (B(SE)= -0.912 (0.043); *p*=0.034). Although components 7 and 16 showed differing correlations with IRI FS (see Table 4), those relationships did not remain significant in the presence of age, sex, or total gray matter volume. Additionally, no other IRI dimension was associated with component 5 in the presence of sex, age, ICV, or total gray matter volume. Examination of the coordinates showing the strongest associations revealed that this component was primarily mid-posterior cingulate and parietal with a few correlations with gray matter in the temporal cortex and frontal cortex as well (see Table 5 for list of regions). The variance explained in IRI PT for this model was R^2=0.045.

3.4. Aim 2 Results—Main Effect IRI, Neurological EP Gray Matter, Age, and Sex Associations with Drinking Variables

We tested a series of regression models using the surviving component from the Aim 1 SBM analyses (component 5) and drinking variables derived from the Form 90, SIP, and PACS. First, testing IRI EC, the main result was a main effect of IRI EC inversely predicting the percentage of heavy drinking days in the 90 days leading up to baseline (see Table 6; B(SE)= -1.57 (0.743); *p*=0.035). Variance explained in total percent heavy drinking days was R^2=0.11. There was also an effect of age positively relating to the percentage of heavy drinking days in the 90 days leading up to baseline (B(SE)= 0.68 (0.279); *p*=0.014). In a regression using this same model to predict the number of drinking days for this dataset, only age was significantly associated with drinking days (B(SE)= 0.56 (0.26); *p*=0.03) while neither sex, IRI EC, nor SBM

component 5 were associated (sex: B(SE)= 9.87 (25.44), p=0.7; IRI EC: B(SE)= -0.85 (0.69), p=0.22; SBM component 5: B(SE)= 0.17 (3.6); p=0.96). The same was true for a regression model predicting percentage of (any) drinking days whereby age was positively associated (B(SE)= 0.62 (0.29); p=0.03), but not sex (B(SE)= 10.97 (28.27); p=0.7), not IRI EC (B(SE)= -0.95 (0.77); p=0.22), nor was SBM component 5 significantly associated (B(SE)= 0.18 (4.004); p=0.96).

Another regression using this IRI EC model to predict number of drinks per drinking day showed that none of our independent variables were associated, including age (B(SE)= 0.04 (0.05); p=0.34), sex (B(SE)= -7.28 (4.56); p=0.11), IRI EC (B(SE)= -0.05 (0.12); p=0.7), nor SBM component 5 (B(SE)= -0.33 (0.65); p=0.61). Further, none of our independent variables showed any main effects predicting total number of drinks consumed (total SEC) in the 90 days leading up to baseline including age (B(SE)= 5.25 (3.22); p=0.1), sex (B(SE)= -504.81 (317.66); p=011), IRI EC (B(SE)= -13.67 (8.59); p=0.11), and SBM component 5 (B(SE)= -24.13 (45.0); p=0.59). There were additionally no relationships between age, sex, IRI EC, or SBM component 5 and craving on the PACS (age: B(SE)= 0.08 (0.06), p=0.16; sex: B(SE)= 1.18 (5.71), p=0.84; IRI EC: B(SE)= -0.2 (0.15), p=0.19; SBM component 5: B(SE)= -0.81 (0.78), p=0.31). However, there was a positive association between age and drinking consequences on the SIP (age: B(SE)= 0.27 (0.07); p<0.001) however, no other variable in the IRI EC regression model associated with total SIP score (sex: B(SE)= 8.19 (7.34); p=0.27, IRI EC: B(SE)= -0.04 (0.2); p=0.82), but SBM component 5 was close (B(SE)= -1.7 (1.01); p=0.09).

Finally, we tested a regression model using IRI PT alongside age, sex, SBM component 5 (and the interactions of IRI PT by sex and SBM component 5 by sex as

reported in the aim 3 results below). Using total craving for alcohol on the PACS as the dependent variable, we found a main effect of IRI PT and a marginal relationship with sex, but no other main effects were significant: (age: B(SE)= 0.06 (0.06); p=0.31; sex: B(SE)= -8.46 (5.07); p=0.1, IRI PT: B(SE)= -0.44 (0.17); p=0.01; SBM component 5: B(SE)= -0.89 (0.77); p=0.25). Replacing total craving with total drinking consequences on the SIP revealed that age was positively associated with total SIP score while none of the other variables were associated: (age: B(SE)= 0.25 (0.07), p<0.001; sex: B(SE)= -6.44 (6.57); p=0.33, IRI PT: B(SE)= -0.4 (0.23); p=0.075; SBM component 5: B(SE)= -1.77 (0.999); p=0.076). Predicting the percentage of heavy drinking days from this regression model also showed that age, but nothing else was significantly and positively related: (age: B(SE)= 0.6 (0.28), p=0.035; sex: B(SE)= -21.01 (26.37); p=0.43, IRI PT: B(SE)= -0.46 (0.89); p=0.6; SBM component 5: B(SE)= -5.54 (3.97); p=0.16).

When testing the number of drinking days as the dependent variable, there were no significant associations with any of the independent, main effect, variables: (age: B(SE)= 0.5 (0.26), p=0.054; sex: B(SE)= -1.2 (24.23); p=0.96, IRI PT: B(SE)= -0.43 (0.82); p=0.6; SBM component 5: B(SE)= 0.12 (3.65); p=0.97). Results were similarly non-significant when testing the number of drinks per drinking day in the 90 days leading up to baseline: (age: B(SE)= 0.04 (0.05), p=0.43; sex: B(SE)= -6.72 (4.28); p=0.12, IRI PT: B(SE)= -0.23 (0.14); p=0.11; SBM component 5: B(SE)= -0.36 (0.65); p=0.58). We found a similar pattern of results while testing the percentage of (any) drinking days in the 90 days leading up to baseline: (age: B(SE)= 0.56 (0.29), p=0.054; sex: B(SE)= -1.34 (26.92); p=0.96, IRI PT: B(SE)= -0.48 (0.53); p=0.6; SBM component 5: B(SE)= 0.14 (4.05); p=0.97). Finally, when we tested total number of drinks in the 90 days leading up

to baseline, there were also no significant associations across all independent variables: (age: B(SE)= 4.35 (3.25), p=0.18; sex: B(SE)= -294.77 (302.17); p=0.33, IRI PT: B(SE)= -11.19 (10.19); p=0.27; SBM component 5: B(SE)= -25.69 (45.47); p=0.57).

We then replaced IRI PT with IRI FS and began testing the main effect associations of this factor predicting each drinking variable alongside, age, sex, and SBM component 5 as additional independent variables in the regression. One of the models using IRI FS showed that this IRI factor positively predicted total craving for alcohol on the PACS in the 90 days leading up to baseline (see Table 6; B(SE)= 0.27 (0.122); p=0.025). Variance explained in total craving was R^2=0.075. Sex was also close to reaching a significant, positive association with total PACS score as well (B(SE)= 5.47 (3.23); p=0.09). Neither age, nor SBM component 5 were associated with total PACS score in this regression (age: B(SE)= 0.09 (0.06); p=0.1; SBM component 5: B(SE)= -0.74 (0.78); p=0.34). When predicting total SIP score using this IRI FS regression model, we found that age significantly and positively associated with drinking consequences on the SIP but no other main effect showed significant associations (age: B(SE)= 0.28 (0.07); p<0.001; sex: B(SE)= 4.42 (4.21); p=0.29, IRI FS: B(SE)= 0.12 (0.16); p=0.45, SBM component 5: B(SE)= -1.67 (1.01); p=0.1).

The IRI FS regression did not show any associations between main effect variables and number of drinking days, either: (age: B(SE)= 0.46 (0.26); p=0.08 sex: B(SE)= 1.94 (15.0); p=0.9, IRI FS: B(SE)= -0.52 (0.59); p=0.38, SBM component 5: B(SE)= 0.08 (3.64); p=0.98). Moreover, there were no associations between IRI FS (or any other of these variables) and number of drinks per drinking day: (age: B(SE)= 0.04 (0.05); p=0.43 sex: B(SE)= -5.12 (2.66); p=0.054, IRI FS: B(SE)= -0.1 (0.105); p=0.34,

SBM component 5: B(SE)= -0.36 (0.64); *p*=0.58). The IRI FS regression also did not show any significant predictions of percentage of drinking days (age: B(SE)= 0.51 (0.29); *p*=0.08 sex: B(SE)= 2.15 (16.66); *p*=0.9, IRI FS: B(SE)= -0.57 (0.66); *p*=0.38, SBM component 5: B(SE)= 0.09 (4.04); *p*=0.98) nor any significant predictions of the percentage of heavy drinking days in the 90 days leading up to baseline (age: B(SE)= 0.52 (0.28); *p*=0.07 sex: B(SE)= -21.61 (16.16); *p*=0.18, IRI FS: B(SE)= -1.11 (0.64); *p*=0.08, SBM component 5: B(SE)= -5.74 (3.92); *p*=0.14). The same results were true of this regression model predicting total number of standard drinks in the 90 days leading up to baseline as well (age: B(SE)= 4.18 (3.28); *p*=0.2 sex: B(SE)= -260.42 (186.82); *p*=0.16, IRI FS: B(SE)= -7.15 (7.35); *p*=0.33, SBM component 5: B(SE)= -26.24 (45.28); *p*=0.56), thus leaving associations with craving on the PACS as the only significant relationships.

Replacing IRI FS with IRI PD in the regression model showed that this factor was also positively related to total craving for alcohol on the PACS in the days in the 90 days leading up to baseline (see Table 6; B(SE)= 0.44 (0.137); *p*=0.001) but no other main effect was associated with the PACS (age: B(SE)= 0.08 (0.05); *p*=0.15; sex: B(SE)= 1.34 (2.34); *p*=0.57, SBM component 5: B(SE)= -0.23 (0.77); *p*=0.77). Variance explained in total craving for this model using IRI PD was also R^2=0.075. Also using IRI PD, we found that this factor was positively related to total drinking consequences on the SIP in the days in the 90 days leading up to baseline (see Table 6; B(SE)= 0.59 (0.174); *p*=0.001) and age was also positively related to total SIP score (B(SE)= 0.28 (0.07); *p*<0.001). Variance explained in total drinking consequences by this model was R^2=0.256. Neither of the other variables showed any main effect relationships with

drinking consequences on the SIP (sex: B(SE)= 2.25 (2.95); *p*=0.45; SBM component 5: B(SE)= -0.93 (0.97); *p*=0.34).

Using this IRI PD regression model we also tested associations with drinking variables derived from the Form 90. When number of drinking days served as the dependent variable, only age was significantly associated: (age: B(SE)= 0.52 (0.26); *p*=0.048; sex: B(SE)= 3.95 (11.37); *p*=0.73, IRI PD: B(SE)= 0.02 (0.67); *p*=0.98, SBM component 5: B(SE)= 0.19 (3.8); *p*=0.73). When testing the percentage of any drinking days in the 90 days leading up to baseline, we found similar results whereby age was the only significant (and positive) association: (age: B(SE)= 0.57 (0.29); *p*=0.048; sex: B(SE)= 4.36 (12.63); *p*=0.73, IRI PD: B(SE)= 0.02 (0.74); *p*=0.98, SBM component 5: B(SE)= 0.21 (4.23); *p*=0.96). This same pattern of results was also found when examining the percentage of heavy drinking days, as well: (age: B(SE)= 0.64 (0.28); *p*=0.024; sex: B(SE)= -3.44 (12.34); *p*=0.78, IRI PD: B(SE)= -0.8 (0.73); *p*=0.27, SBM component 5: B(SE)= -6.79 (4.13); *p*=0.1). When testing the number of drinks per drinking day however, there were no main effects at all: (age: B(SE)= 0.05 (0.05); *p*=0.34; sex: B(SE)= -1.26 (2.03); *p*=0.54, IRI PD: B(SE)= 0.01 (0.12); *p*=0.92; SBM component 5: B(SE)= -0.32 (0.68); *p*=0.64). We found this same profile of results when testing total number of drinks in the 90 days leading up to baseline as the dependent variable, as well: (age: B(SE)= 4.78 (3.27); *p*=0.14; sex: B(SE)= -24.14 (142.41); *p*=0.87, IRI PD: B(SE)= -2.02 (8.39); *p*=0.81; SBM component 5: B(SE)= -27.91 (47.65); *p*=0.56).

3.5. Aim 3 Results—Interaction between IRI and Sex Associations with Drinking Variables

While section 3.4 details the main effect results under Aim 2, in each of the regression models above, we also tested the effect of interaction terms for the IRI by sex and SBM component 5 by sex predicting each of the drinking variables discussed previously. Beginning with IRI EC's regression model and using percent heavy drinking days as the dependent variable (with age, sex, IRI EC, SBM component 5, IRI EC*sex, and SBM component 5*sex as independent), we found that the interaction of IRI EC and sex nearly predicted percentage of heavy days but did not reach significance and neither did the interaction of SBM component 5 and sex: (IRI EC*sex: B(SE)= 2.19 (1.24); p=0.08; SBM component 5*sex: B(SE)= 2.33 (5.63); p=0.68). There were no interaction results using IRI EC to predict the number of drinking days: (IRI EC*sex: B(SE)= -0.1 (1.15); p=0.93; SBM component 5*sex: B(SE)= -1.61 (5.21); p=0.76), nor were there results using this model to predict number of drinks per drinking day: (IRI EC*sex: B(SE)= 0.28 (0.21); p=0.17; SBM component 5*sex: B(SE)= 0.41 (0.93); p=0.66), percent drinking days: (IRI EC*sex: B(SE)= -0.11 (1.27); p=0.93; SBM component 5*sex: B(SE)= -1.78 (5.79); p=0.76), total SEC: (IRI EC*sex: B(SE)= 23.83 (14.3); p=0.096; SBM component 5*sex: B(SE)= 1.43 (65.05); p=0.98), nor total PACS score: (IRI EC*sex: B(SE)= 0.03 (0.257); p=0.91; SBM component 5*sex: B(SE)= 0.74 (1.11); p=0.91), or total SIP score: (IRI EC*sex: B(SE)= -0.24 (0.33); p=0.47; SBM component 5*sex: B(SE)= 0.63 (1.43); p=0.67).

We also tested a model using IRI PT which was significantly and inversely associated with the SBM gray matter component number 5 from the Aim 1 analyses

(section 3.3 above), even in the presence of covariates and also showed a main effect of IRI PT inversely relating to alcohol craving on the PACS from the Aim 2 analyses (section 3.4 above). There was also a significant interaction of IRI PT by sex predicting total craving (B(SE)= -0.48 (0.243); *p*=0.049; see Table 6). This prompted a simple slopes analysis grouping by sex as reported below. Variance explained in the PACS for the interaction model was R^2= 0.087. Simple slopes showed that IRI PT was inversely related to total craving for men (B(SE)= -0.46 (0.154); *p*=0.003), but not women (B(SE)= 0.027 (0.186); *p*=0.886; see Figure 6). Also interesting is that the variance explained in craving for men was R^2=0.147, while the variance explained in craving for women was R^2=0.067.

The interactions of IRI PT*sex and SBM component 5*sex were not related to any other drinking variables, including drinking consequences on the SIP (IRI PT*sex: B(SE)= 0.44 (0.32), *p*=0.16; SBM component 5*sex: B(SE)= 1.17 (1.41); *p*=0.41), number of drinking days (IRI PT*sex: B(SE)= 0.32 (1.16); *p*=0.79; SBM component 5*sex: B(SE)= -0.47 (5.2); *p*=0.93), number of drinks per drinking day (IRI PT*sex: B(SE)= 0.28 (0.21); *p*=0.17; SBM component 5*sex: B(SE)= 0.19 (0.92); *p*=0.84), percentage of drinking days (IRI PT*sex: B(SE)= 0.35 (1.29); *p*=0.79; SBM component 5*sex: B(SE)= -0.52 (5.77); *p*=0.93), or percentage of heavy drinking days: (IRI PT*sex: B(SE)= 1.24 (1.26); *p*=0.33; SBM component 5*sex: B(SE)= 2.35 (5.65), *p*=0.68), or total SEC: (IRI PT*sex: B(SE)= 14.38 (14.43); *p*=0.32; SBM component 5*sex: B(SE)= -6.57 (64.79); *p*=0.92).

Although the main effect of IRI FS was related to total alcohol craving on the PACS, there were no interaction results relating to this measure: (IRI FS*sex: B(SE)=

-0.27 (0.18); *p*=0.14; SBM component 5*sex: B(SE)= 0.92 (1.06); *p*=0.39). There were no interaction results between IRI FS and sex, nor SBM component 5 by sex for total SIP score (IRI FS*sex: B(SE)= -0.11 (0.24); *p*=0.63; SBM component 5*sex: B(SE)= 0.99 (1.39); *p*=0.47), number of drinking days (IRI FS*sex: B(SE)= 0.24 (0.86); *p*=0.78; SBM component 5*sex: B(SE)= -0.37 (5.13); *p*=0.94), number of drinks per drinking day (IRI FS*sex: B(SE)= 0.25 (0.15); *p*=0.098; SBM component 5*sex: B(SE)= 0.18 (0.91); *p*=0.84), percentage of drinking days (IRI FS*sex: B(SE)= 0.27 (0.95); *p*=0.78; SBM component 5*sex: B(SE)= -0.41 (15.7); *p*=0.94), percentage of heavy drinking days (IRI FS*sex: B(SE)= 1.61 (0.92); *p*=0.08; SBM component 5*sex: B(SE)= 1.98 (5.53); *p*=0.72), nor total SEC in the 90 days leading up to baseline (IRI FS*sex: B(SE)= 15.75 (10.68); *p*=0.14; SBM component 5*sex: B(SE)= -6.92 (63.94); *p*=0.91).

Similar to FS, IRI PD showed a main effect association with craving on the PACS as discussed in section 3.4 above, but did not significantly interact with sex, nor did SBM component 5 in this regression model: (IRI PD*sex: B(SE)= -0.12 (0.23); *p*=0.6; SBM component 5*sex: B(SE)= 0.28 (1.04); *p*=0.79). Results were similarly non-significant when analyzing total SIP score as the dependent variable instead: (IRI PD*sex: B(SE)= -0.11 (0.29); *p*=0.7; SBM component 5*sex: B(SE)= 0.06 (1.32); *p*=0.96). There were additionally no significant interactions findings using IRI PD by sex (or SBM component 5 by sex) when testing the number of drinking days (IRI PD*sex: B(SE)= 0.12 (1.08); *p*=0.91; SBM component 5*sex: B(SE)= -0.53 (5.29); *p*=0.92), number of drinks per drinking day (IRI PD*sex: B(SE)= 0.25 (0.15); *p*=0.1; SBM component 5*sex: B(SE)= 0.18 (0.91); *p*=0.84), percentage of drinking days (IRI PD*sex: B(SE)= 0.13 (1.2); *p*=0.91; SBM component 5*sex: B(SE)= -0.59 (5.87); *p*=0.92), percentage of heavy

drinking days (IRI PD*sex: B(SE)= 0.95 (1.18); p=0.42; SBM component 5*sex: B(SE)= 2.79 (5.74); p=0.63), or total number of drinks/total SEC in the 90 days leading up to baseline (IRI PD*sex: B(SE)= 2.79 (13.58); p=0.84; SBM component 5*sex: B(SE)= -7.8 (66.23); p=0.91).

4. Discussion

The goals of this project included determining the gray matter associations with the IRI in this heavy drinking sample (Aim 1). We then related the best representation of neurological EP-associated gray matter and the IRI with drinking variables for Aim 2. Finally, we investigated relevant interactions between the IRI, EP-related gray matter, drinking outcomes, and interactions with sex (Aim 3). For the discussion of Aim 1, we describe gray matter associations with the IRI, then for Aim 2 discuss main effect associations of the IRI with drinking variables. Last, for Aim 3, we discuss the interaction results in the context of previous interaction findings in prior studies.

4.1. Aim 1—Gray Matter (GM) Associations of the Interpersonal Reactivity Index (IRI)

The first aim of the current study was to investigate the GM associations with the IRI. Results from the VBM indicated no significant associations between GM and the IRI factors and only age and intracranial volume (ICV) were significantly associated with GM. These findings are consistent with Good and colleagues (2001) who similarly found inverse relationships between age and voxel-wise GM in the frontal cortex in healthy samples. Similarly, larger ICV was positively associated with GM across the brain. This is at least partially in line with analyses by Sluming and colleagues (2002) studying gray matter in musicians. They found that total gray matter volume was highly correlated with cerebral gray matter volume in both musicians and healthy controls. Both gray matter and white matter show similarly strong and positive correlations with total gray matter volume for both healthy men and women (Gur et al., 1999). This also follows previous

research arguing that brain growth drives the growth of the skull; hence, head size should be dependent upon brain size, and age and head size should both account for unique variance in cortical gray matter (Pfefferbaum, et al., 1994).

The SBM results provided the main findings for aim 1. Using SBM, we found inverse associations between IRI PT and an independent component containing the posterior cingulate, bilateral parietal, bilateral mid-temporal, and bilateral mid-frontal regions as well as the IFG. This association remains even after controlling for age, sex, and total gray matter or intracranial volume, which is a more detailed level of control of covariates than in previous drinking samples (Schmidt et al., 2017). The inferior frontal cortex, precuneus, temporoparietal junction, and anterior cingulate have all been associated with taking the perspectives of others (Jackson et al., 2005; 2006; Van Overwalle & Baetens, 2009; Banissy et al., 2012). Mid-frontal, inferior frontal, and mid-temporal regions as well as the posterior cingulate have also been implicated in effortful perspective taking (Amodio & Frith, 2006; Frith & Frith, 2007). Therefore, it makes sense that component 5 would significantly predict IRI PT.

To our knowledge, the only study that has found significant GM and IRI associations in an AUD sample (Schmidt et al., 2017) used cortical thickness (CT) values in a bivariate correlational analysis with the IRI factors. Their results indicated positive associations between frontal CT and IRI PT. However, their associations in an AUD sample are based on less than 15 people for that group and only bivariate correlations with cortical thickness, while our correlated associations were backed up by testing regression associations while controlling for covariates (in particular age and sex). The final component showing an association with any of the IRI dimensions even in the

presence of covariates was SBM gray matter component 5, which was made up of familiar members of the effortful aspects of empathic processing areas: the mid/posterior cingulate, the angular gyrus, the cuneus and precuneus, the inferior and mid parietal cortices, bilateral mid-temporal gray matter, and bilateral triangular portions of the inferior frontal gyri. Many of the regions identified in gray matter component 5 have been implicated in differing aspects of effortful empathic processing. Thus, the results are consistent with other studies examining neural correlates of EP.

4.2. Aim 2—Main Effect Associations with Drinking Variables

IRI EC was inversely associated with the percentage of heavy drinking days leading up to baseline while IRI FS and IRI PD were positively associated with craving for men and women. Across all possible drinking outcomes, including heavy drinking, total alcohol consumption, and consequences, only older age was associated with more drinking consequences for the entire sample. A number of studies have documented deficits in emotional processing for samples with AUD compared to healthy controls (Frigerio et al., 2002; Dethier & Blairy, 2012; Ferrari et al., 2014; Maurage et al., 2015). It makes sense then, that in a heavy drinking sample, the percentage of heavy drinking days would inversely relate to self-reported EC in that there seems to be a consistent negative relationship between heavy drinking and emotional processing across samples. Further, the other affective factor of the IRI—PD—has been associated with neuroticism in a methadone in-treatment sample previously, (Alterman et al., 2003) which may shed light on why this factor was positively related to more craving for alcohol in our own sample. Greater personal distress in relation to the suffering of others may drive greater craving for alcohol or other substances in general.

Goldstein and colleagues (2009) suggested that continuous alcohol consumption may redirect interoceptive cues away from a person attending to their own bodily well-being and instead cause them to hyper-focus on craving for alcohol, which may be related to insular activity (Contreras et al., 2007; Naqvi & Bechara, 2009; 2010). This follows Schmidt & colleagues (2017) who found positive associations between cortical thickness in the insula and FS on the IRI, suggesting the insula is still involved in the simulation of experiences in an AUD sample. Our own analyses showed that FS and craving are related for heavy drinkers who all meet criteria for AUD, which follows (Goldstein et al., 2009) who suggests that craving is a function of paying more attention to the desire for alcohol than other bodily states (and possibly the affect of others as per Craig, 2008). Put simply, individuals high in FS who are also heavy drinking may actually be more prone to simulating the experiences of craving, which may lead to more drinking. The presence of a positive relationship between craving and FS in this dataset may signal that individuals higher in the ability to simulate experiences might channel those resources into the subjective experience of craving.

Taken together, we show that gray matter in the posterior/mid cingulate, parietal cortex, temporal cortex, and frontal cortex related to IRI PT, which in turn related to less craving as a main effect for the whole sample, such that areas involved in effortful empathic processing / perspective-taking behavior may be related to less self-reported craving. Additionally, considering that more EC predicted a lower percentage of heavy drinking days, but more fantasy simulation (FS) and personal distress about the suffering of others (PD) relates to more craving, may indicate that it is not simply more empathic processing that relates to less drinking. Rather, a non-distressful empathic processing that

focuses on the harm done to others without causing psychological harm to oneself may be associated with better drinking behavior. Put simply, the type of empathic processing that over-identifies a person with others' distress may encourage unhealthy coping mechanisms.

4.3. Aim 3—Interaction Associations with Drinking Variables

The interaction of IRI PT and sex showed a significant and inverse relationship with self-reported alcohol craving. Simple slopes tests of that interaction revealed that greater scores on IRI PT were related to a less craving specifically for males in the sample, but not females. These results replicate a previous finding by our lab (Robinson et al., 2018) that self-reported EP and social support by family were inversely related to drinking in men but not women. Additionally, although women scored higher on IRI EC and FS there were no statistical differences between men and women on IRI PD or PT, nor were there sex differences on drinking variables or drinking consequences although mean scores for women on the SIP were somewhat higher. This may not be surprising in that sex differences on drinking appear to be age-cohort related and male-female differences on drinking may be declining for younger samples (Keyes et al., 2008).

What is interesting is that men and women scored similarly on perspective taking in this sample, and empathic concern is related to less drinking for men and women, but perspective taking is specifically inversely related to craving in men. The fact that a more effortful side of empathic processing may be specifically impactful for men may actually shed light on why previous research has found conflicting findings using the IRI in drinking samples. For example, in an earlier study by Maurage and colleagues, (2011),

lower scores on the empathic concern and personal distress scales of the IRI were found in 30 in-patients for AUD (12 women) compared to healthy controls, while perspective taking and fantasy simulation showed null-results. Alternatively, this same research group also found that 34 in-patients with AUD (8 women) showed lower scores on perspective taking only (compared to matched controls; Maurage et al., 2015). If true that perspective taking is an additionally relevant predictor of less drinking in men as evidenced in the current study, then sampling error and underrepresentation of females could play a large part in why these varying findings occur using the IRI.

To date, the only paper that we know of investigating gray matter sex differences in relation to the IRI is Cheng and colleagues (2009) who found only positive associations between largely frontal gray matter regions and IRI EC for both healthy men and women. Highly similar frontal regions were associated with IRI EC in our own sample. Banissy and colleagues (2012) found only inverse associations between IRI EC and gray matter in the insula, anterior cingulate, and precuneus using VBM, but did not report any sex differences in a healthy sample of 52 men and 66 women.

The presence of heavy drinking in our sample may have a downstream effect on pre-existing sex differences on EP. There is modest evidence that gray matter loss in the presence of heavy alcohol use is worse for females than for males and using SBM, prior studies have found slightly different areas of degeneration for each of the sex groups (Thayer et al., 2016). Additionally, gray matter in EP-related regions is not the only factor related to EP. Findings by Parkinson and Wheatley (2014) recently showed that IRI EC could be predicted by functional anisotropy scores in white matter tracts between many of these gray matter areas discussed presently.

4.4. Limitations

The current project had several notable limitations, one of which was the collinearity between age, sex, and intracranial volume and gray matter volume likely caused by sampling in this study. With fewer women in the dataset at older ages, sex and age were moderately correlated. In addition, sex and both intracranial volume and gray matter volume were highly collinear which tended to introduce multicollinearity concerns. Additional limitations include being unable to resolve preprocessing errors in the imaging data, having failed to include all participants' Form 90 data due to time constraints, and the resulting possibility that this may have reduced power to detect some of the effects.

Despite this, post-hoc power analyses in G*Power using the observed semi-partial R^2 in our study for IRI EC*sex predicting percent heavy drinking days revealed that the a priori power analysis was correct in that only N=44 were required for 80% power to detect an effect. While it may be tempting to make causal explanations from the current project, this cannot be done without experimental and preferably longitudinal data. Because the ABQ DrinQ project is ongoing and longitudinal, there is still potential for future analyses of this dataset to determine how EP may associate with drinking change over time.

5. Conclusion

The current study found support for an inverse association between percentage of heavy drinking days and IRI EC for men and women as well as an inverse relationship of IRI PT and self-reported craving for alcohol for men only, replicating previous research from our lab (Robinson et al., 2018). Gray matter was related to IRI PT in mainly temporoparietal and some frontotemporal regions that have been typically associated with effortful attempts to take the perspectives of others (Jackson et al., 2005; 2006; Van Overwalle & Baetens, 2009; Banissy et al., 2012; Amodio & Frith, 2006; Frith & Frith, 2007).

Overall, women scored higher than men on IRI EC, but not IRI PT, and also did not differ from men on drinking; yet, higher IRI PT scores were only related to less drinking for men suggesting, like previous research, that aspects of more effortful empathic processing may be useful to further examine in men. These results may help to explain why treatment-seeking samples that contain more women show differences on IRI EC (Maurage et al., 2011), while samples containing a higher proportion of men seem to show differences compared to controls on IRI PT (Maurage et al., 2015). Future research should make use of functional tasks relating to both effortful EP such as perspective taking methods employed by Saxe & Wexler (2005) as well as tasks investigating the automatic and emotional side of EP such as methods by Jackson et al., (2006) among others. All future research in this line of work should also pay strong attention to sampling by sex to unravel sex differences further.

Table 1—List of Social Brain Atlas Regions by Coordinate and Label

Region	**Label**	**x**	**y**	**z**
Right inferior frontal gyrus	IFG_R	48	24	2
Left hippocampus	HC_L	-24	-18	-17
Right hippocampus	HC_R	25	-19	-15
Rostral anterior cingulate cortex	rACC	-3	41	4
Ventromedial prefrontal cortex	vmPFC	2	45	-15
Right amygdala	AM_R	23	-3	-18
Left amygdala	AM_L	-21	-4	-18
Left nucleus accumbens	NAC_L	-13	11	-8
Right nucleus accumbens	NAC_R	11	10	-7
Left middle temporal gyrus	MTG_L	-56	-14	-13
Left Precuneus	Left Prec	-1	-59	41
Right temporo-parietal junction	TPJ_R	54	-55	20
Right middle temporal gyrus	MTG_R	56	-10	-17
Left temporal pole	TP_L	-48	8	-36
Right temporal pole	TP_R	53	7	-26
Medial frontal pole	FP	1	58	10
Posterior cingulate cortex	PCC	-1	-54	23
Dorsomedial prefrontal cortex	dmPFC	-4	53	31
Left temporo-parietal junction	TPJ_L	-49	-61	27
Posterior mid-cingulate cortex	pMCC	-3	-29	32
Left middle temporal V5 area	MT/V5_L	-50	-66	5
Right middle temporal V5 area	MT/V5_R	50	-66	6
Left fusiform gyrus	FG_L	-42	-62	-16
Right fusiform gyrus	FG_R	43	-57	-19
Left posterior superior temporal sulcus	pSTS_L	-56	-39	2
Right posterior superior temporal gyrus	pSTS_R	54	-39	0
Left supplementary motor area	SMA_L	-41	6	45
Left anterior insula	AI_L	-34	19	0
Right supramarginal gyrus	SMG_R	54	-30	38
Right cerebellum	Cereb_R	28	-70	-30
Left cerebellum	Cereb_L	-21	-66	-35
Right anterior insula	AI_R	38	18	-3
Left supramarginal gyrus	SMG_L	-41	-41	42
Right supplementary motor area	SMA_R	48	6	35
Left inferior frontal gyrus	IFG_L	-45	27	-3
Left inferior parietal lobe	IPL_L	-43	-36	41
Anterior mid-cingulate cortex	aMCC	1	25	30

Note: This table shows the list of regions found to be associated with various social-related tasks (Alcala-Lopez et al., 2017). Coordinates are in MNI-152 space.

Table 2—Sex Differences on the Interpersonal Reactivity Index

IRI Dimension	Grandmean (SD)	Mean (SD) Males	Mean (SD) Females	t-test; sex diffs.	p-value
EC	**21.18 (4.66)**	**19.95 (4.77)**	**22.75 (4.04)**	**-3.63**	**<0.001**
FS	**15.96 (5.99)**	**14.62 (5.87)**	**17.65 (5.74)**	**-3.02**	**0.003**
PT	20.1 (4.52)	20.29 (3.97)	19.85 (5.15)	0.562	0.575
PD	8.71 (5.04)	7.74 (5.17)	9.95 (4.62)	-2.597	0.01
SPF-EC	12.12 (2.78)	11.47 (2.9)	12.93 (2.41)	-3.134	0.002
SPF-FS	10.92 (4.95)	10.0 (4.88)	12.08 (4.83)	-2.482	0.014
SPF-PT	14.99 (3.46)	15.30 (2.98)	14.6 (3.97)	1.179	0.241
SPF-PD	6.31 (3.79)	5.64 (3.94)	7.15 (3.43)	-2.34	0.021

Note: The degrees of freedom for all t-tests reported were df=134. A Sidak correction for the 0.05 alpha level was used, accounting for four comparisons (comparing the means for males and females on each dimension of the IRI) with bold denoting a t-test surviving the Sidak-corrected alpha level of 0.012. SPF results are only reported here for the sake of comparison but all conclusions were drawn from the full IRI items for each dimension (and therefore we only corrected for four comparisons). There were no sex differences on any drinking variables that would have survived the Sidak correction or any other correction for multiple comparisons. These contrasts show that EC and FS, show sex differences whereby women score higher than men however this is not true for IRI PT or Sidak-corrected PD.

Table 3—Regions Significantly Predicted by Age from Voxel Based Morphometry

T	P_FWE	x	y	z	region
7.07	<0.001	0	-2	12	Thalamus_R
6.39	<0.001	0	62	24	Frontal_Sup_Medial_L
6.32	<0.001	0	34	28	Cingulum_Ant_L
5.95	0.001	2	62	2	Frontal_Sup_Medial_R
5.87	0.001	-26	62	18	Frontal_Sup_L
5.79	0.002	-30	64	10	Frontal_Sup_L
5.74	0.002	6	-80	-20	Cerebelum_Crus1_R
5.49	0.005	-4	-80	-22	Cerebelum_Crus2_L
5.44	0.006	-18	-24	78	Paracentral_Lobule_L
5.4	0.007	28	24	56	Frontal_Mid_R
5.36	0.008	-48	26	-14	Frontal_Inf_Orb_L
5.35	0.008	28	58	24	Frontal_Mid_R
5.28	0.011	10	48	4	Frontal_Sup_Medial_R
5.24	0.012	-26	14	62	Frontal_Mid_L
5.17	0.016	0	-30	0	Vermis_3
5.15	0.017	-38	-42	-42	Cerebelum_8_L
5.13	0.018	-38	4	-18	Temporal_Pole_Sup_L
5.12	0.019	-48	12	2	Frontal_Inf_Oper_L
5.12	0.019	2	-32	48	Cingulum_Mid_R
5.1	0.02	0	8	66	Supp_Motor_Area_L

Note: Shows the significant peak coordinates of gray matter volume that were inversely associated with age in this dataset. Labels were assigned in R using the MNI-2-AAL database (https://github.com/yunshiuan/label4MRI) of coordinates and labels which corresponds to labels in MRIcron.

Table 4—Source-Based Morphometry Independent Component Correlations with the IRI and Drinking Variables

Factor/Comp. r	IRI EC	IRI PT	IRI FS	IRI PD	Total SEC	NDDD	PDD	PHD	SIP	PACS
SBM Comp. 1 r	0.003	-0.006	0.16	0.142	-0.12	-0.056	-0.17	**-0.25***	-0.032	-0.067
SBM Comp. 2 r	0.098	0.072	0.057	-0.089	-0.5	-0.091	0.052	0.095	-0.043	-0.041
SBM Comp. 3 r	-0.015	0.043	0.153	0.144	-0.001	-0.023	-0.12	-0.053	0.05	0.106
SBM Comp. 4 r	-0.013	0.043	0.112	0.079	-0.023	-0.023	-0.033	0.108	0.091	0.133
SBM Comp. 5 r	-0.15	**-0.21***	-0.04	-0.08	-0.072	-0.046	0.025	-0.136	-0.12	-0.039
SBM Comp. 6 r	0.150	0.177	0.056	0.02	0.29	0.137	-0.167	-0.05	0.107	0.016
SBM Comp. 7 r	-0.003	0.05	**-0.22***	-0.12	0.031	0.018	0.127	0.117	-0.004	0.036
SBM Comp. 8 r	-0.015	-0.009	0.173	0.149	-0.045	-0.044	-0.117	-0.067	0.038	0.046
SBM Comp. 9 r	-0.08	-0.083	0.152	0.066	-0.078	0.024	-0.153	-0.175	-0.094	-0.085
SBM Comp. 10 r	-0.076	0.075	0.069	0.176	-0.079	-0.076	-0.164	-0.038	0.006	0.036
SBM Comp. 11 r	-0.047	-0.065	-0.106	-0.078	0.029	0.125	-0.023	0.03	**-0.2***	**-0.199***
SBM Comp. 12 r	0.108	-0.152	0.131	-0.004	-0.071	-0.028	-0.017	-0.105	-0.172	-0.086
SBM Comp. 13 r	-0.086	0.005	-0.068	-0.034	-0.13	-0.076	-0.083	-0.125	-0.157	-0.141
SBM Comp. 14 r	0.032	-0.025	-0.07	-0.006	0.037	0.036	0.085	0.12	0.047	0.12

SBM Comp. 15										
r	0.069	0.066	0.033	0.026	0.078	0.091	0.047	-0.013	0.012	-0.012
SBM Comp. 16										
r	0.09	0.04	**0.21***	0.16	-0.016	0.058	-0.17	-0.115	-0.023	0.061
SBM Comp. 17										
r	0.005	0.151	0.077	0.014	-0.014	-0.021	-0.108	-0.152	0.007	0.067
SBM Comp. 18										
r	-0.001	0.021	-0.094	-0.1	-0.003	0.105	-0.114	0.043	0.05	-0.001
SBM Comp. 19										
r	0.082	0.124	0.024	-0.11	**0.213***	**0.025***	0.078	0.171	0.03	0.092
SBM Comp. 20										
r	-0.002	-0.042	0.116	0.154	0.072	0.029	0.033	0.028	0.072	0.106

Note: IRI EC: Empathic Concern; IRI FS: Fantasy Simulation; IRI PT: Perspective Taking; IRI PD: Personal Distress; total SEC: total number of standard drinks; NDDD: number of drinks per drinking day; PDD: percentage of drinking days; PHD: percentage of heavy drinking days; PACS: alcohol craving; SIP: drinking consequences. The number of drinking days was not correlated with any of the SBM components and is therefore not reported to conserve space. Out of 20 estimated whole-brain SBM components, only components 5, 7, and 16 correlated with the IRI (or SPF) dimensions. No other correlations reached significance. Subsequent analyses using regression paths and controlling for age, sex, and total gray matter volume revealed that the associations with IRI FS were spurious, however, the association between IRI PT and SBM component 5 remained.

Table 5—Regions of Interest in SBM Component Number Five by Label and Coordinate

Region	x	y	z	Estimated Distance from Closest Label in mm^3
Precuneus_L	-4	-58	24	0
Parietal_Sup_L	-34	-58	60	0
Angular_R	36	-46	34	4.69041576
Frontal_Mid_L	-32	30	34	0
Postcentral_R	52	-20	32	0
Temporal_Mid_L	-48	-22	-8	1
Postcentral_L	-50	-22	34	0
Parietal_Inf_L	-52	-36	54	0
Parietal_Inf_R	34	-46	40	0
Frontal_Mid_R	32	30	24	0
Frontal_Inf_Tri_R	46	16	26	0
Rectus_R	2	16	-22	1
Vermis	0	-70	-46	4.242640687
Cuneus_L	-16	-70	22	0
Cingulum_Mid_R	8	-46	38	0
Cingulum_Mid_L	-6	-46	38	0
Frontal_Inf_Tri_L	-36	42	8	0
Precuneus_R	4	-42	52	0

Note: This table shows the primary regions comprising the whole-brain SBM GM component 5 that was significantly associated with the IRI PT scale and their coordinates in MNI space. The regions are made up primarily of parietal regions, posterior cingulate regions, mid-temporal regions, bilateral mid-frontal cortex, and the bilateral inferior frontal gyrus. Labels were assigned in R using the MNI-2-AAL database (https://github.com/yunshiuan/label4MRI) of coordinates and labels which corresponds to labels in MRIcron.

Table 6—Regression Effects Within Each Analysis Showing Results

Aim Tested	Effect Tested	B(SE), *p*	β
2	**% Heavy Days on IRI EC**	**(B(SE)= -1.57 (0.743); *p*=0.035)**	**-0.27**
2	% Heavy Days on Component 5	(B(SE)= -5.46 (3.89); *p*=0.160)	-0.19
2	% Heavy Days on Sex	(B(SE)= -41.05 (27.48); *p*=0.160)	-0.74
2	**% Heavy Days on Age**	**(B(SE)= 0.68 (0.28); *p*=0.014)**	**0.24**
3	% Heavy Days on IRIEC*Sex	(B(SE)= 2.19 (1.24); *p*=0.077)	0.93
3	% Heavy Days on Component 5*Sex	(B(SE)= 2.33 (5.63); *p*=0.679)	0.06
2	**Total PACS on IRI FS**	**(B(SE)= 0.27 (1.22); *p*=0.025)**	**0.29**
2	Total PACS on Component 5	(B(SE)= -0.74 (1.22); *p*=0.339)	-0.13
2	Total PACS on Sex	(B(SE)= 5.47 (3.23); *p*=0.09)	0.48
2	Total PACS on Age	(B(SE)= 0.091 (0.056); *p*=0.102)	0.16
3	Total PACS on IRIFS*Sex	(B(SE)= -0.27 (0.18); *p*=0.141)	-0.46
3	Total PACS on Component 5*Sex	(B(SE)= 0.92 (1.06); *p*=0.388)	0.12
2	**Total PACS on IRI PD**	**(B(SE)= 0.44 (0.14); *p*=0.001)**	**0.39**
2	Total PACS on Component 5	(B(SE)= -0.23 (0.77); *p*=0.77)	-0.04
2	Total PACS on Sex	(B(SE)= 1.34 (2.34); *p*=0.57)	0.12
2	Total PACS on Age	(B(SE)= 0.08 (0.05); *p*=0.147)	0.13
3	Total PACS on IRIPD*Sex	(B(SE)= -0.12 (0.23); *p*=0.603)	-0.12
3	Total PACS on Component 5*Sex	(B(SE)= 0.28 (1.04); *p*=0.787)	0.04
2	**Total SIP on IRI PD**	**(B(SE)= 0.59 (0.17); *p*=0.001)**	**0.38**
2	Total SIP on Component 5	(B(SE)= -0.93 (0.97); *p*=0.342)	-0.12
2	Total SIP on Sex	(B(SE)= 2.25 (2.95); *p*=0.446)	0.15
2	**Total SIP on Age**	**(B(SE)= 0.28 (0.067); *p*<0.001)**	**0.36**
3	Total SIP on IRIPD*Sex	(B(SE)= -0.11 (0.29); *p*=0.697)	-0.09
3	Total SIP on Component 5*Sex	(B(SE)= 0.06 (1.32); *p*=0.962)	0.006
2	**Total PACS on IRI PT**	**(B(SE)= -0.44 (0.17); *p*=0.011)**	**-0.35**
2	Total PACS on Component 5	(B(SE)= -0.89 (0.77); *p*=0.248)	-0.16
2	Total PACS on Sex	(B(SE)= -8.46 (5.07); *p*=0.095)	-0.75
2	Total PACS on Age	(B(SE)= 0.06 (0.06); *p*=0.310)	0.1
3	**Total PACS on IRIPT*Sex**	**(B(SE)= 0.48 (0.24); *p*=0.049)**	**0.9**
3	Total PACS on Component 5*Sex	(B(SE)= 1.14 (1.09); *p*=0.3)	0.15

Note: This table shows each effect within each regression analysis from which final conclusions are drawn. Main effect results correspond with the testing of aim 2 while interaction results correspond with the testing of aim 3. Bold denotes significant effect.

Figure 1. Regions of Interest in Empathic Processing Abilities

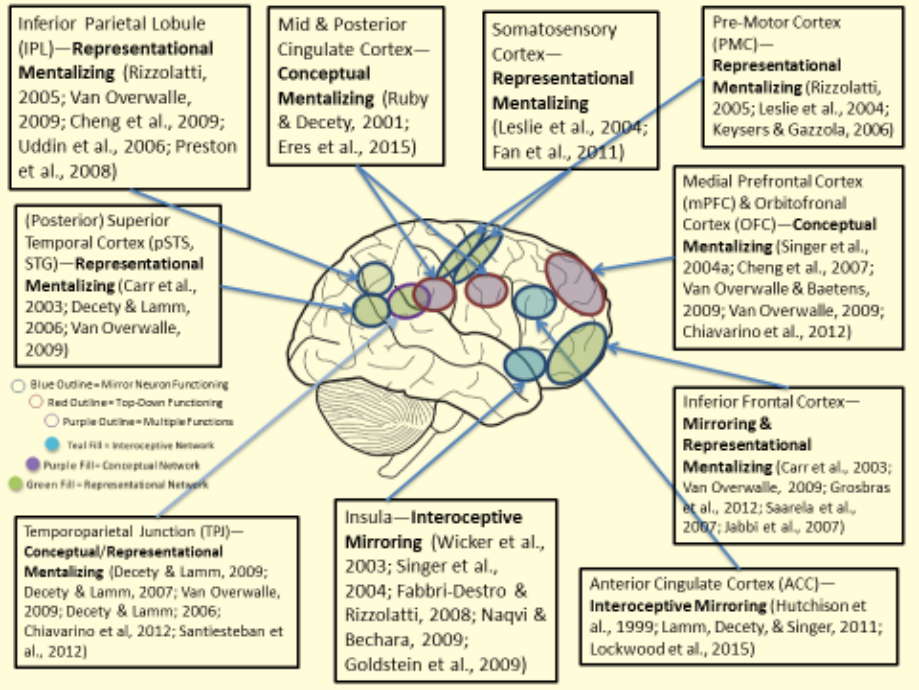


Figure 2. Regions of Interest in Overlap between EP and Alcohol Use Disorder

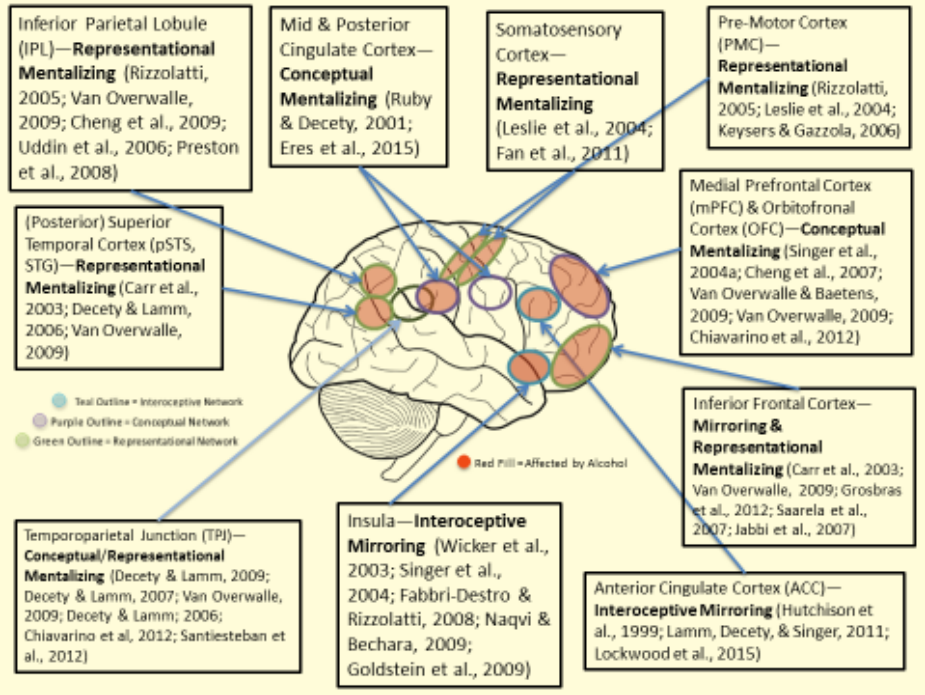
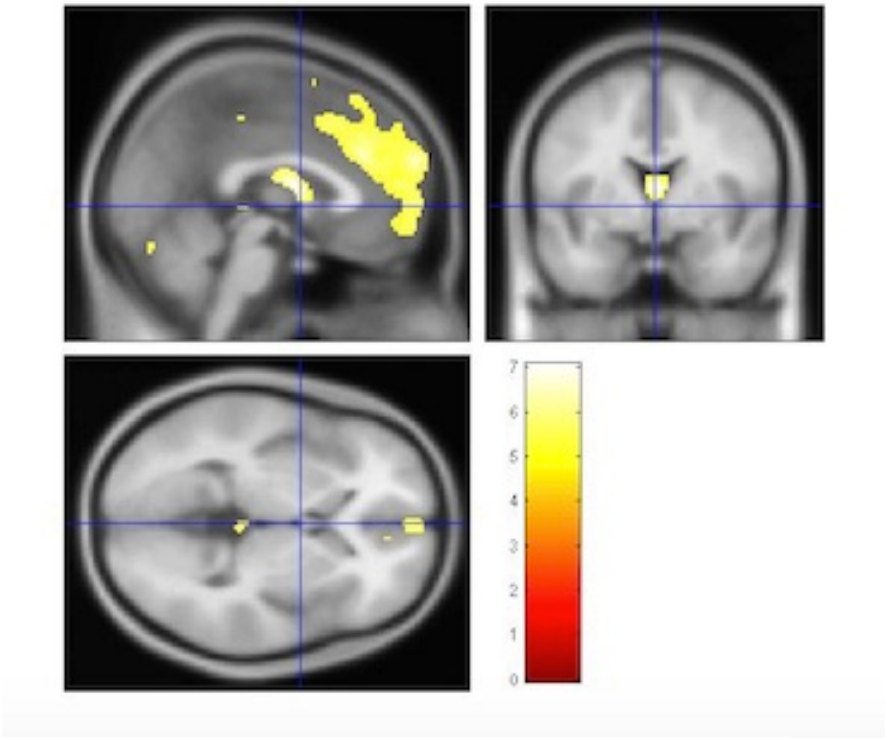


Figure 3—Negative Effect of Age on Gray Matter Volume via Voxel Based Morphometry (Above) Compared to Good & colleagues (2001, p. 30; Below)



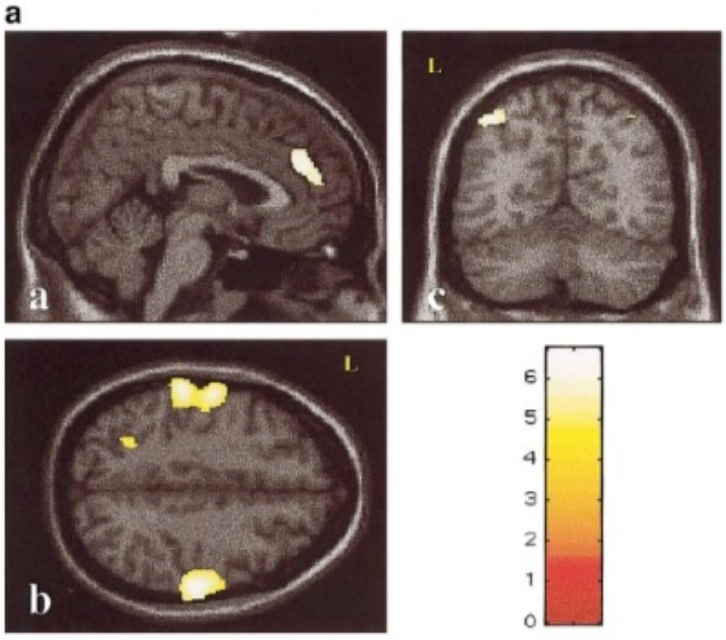


Figure 4—Positive Effect of Greater Intracranial Volume Relating to Greater Gray Matter Volume, Slices in the Axial View

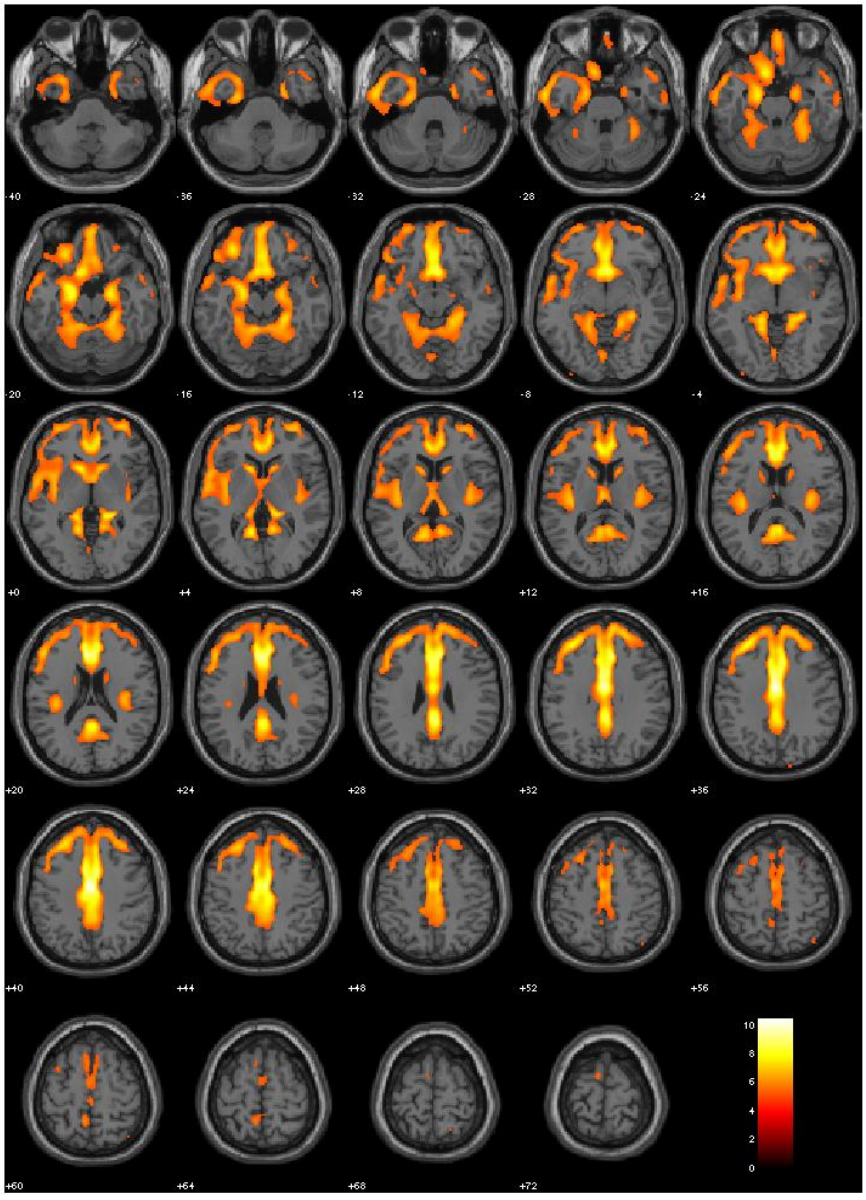
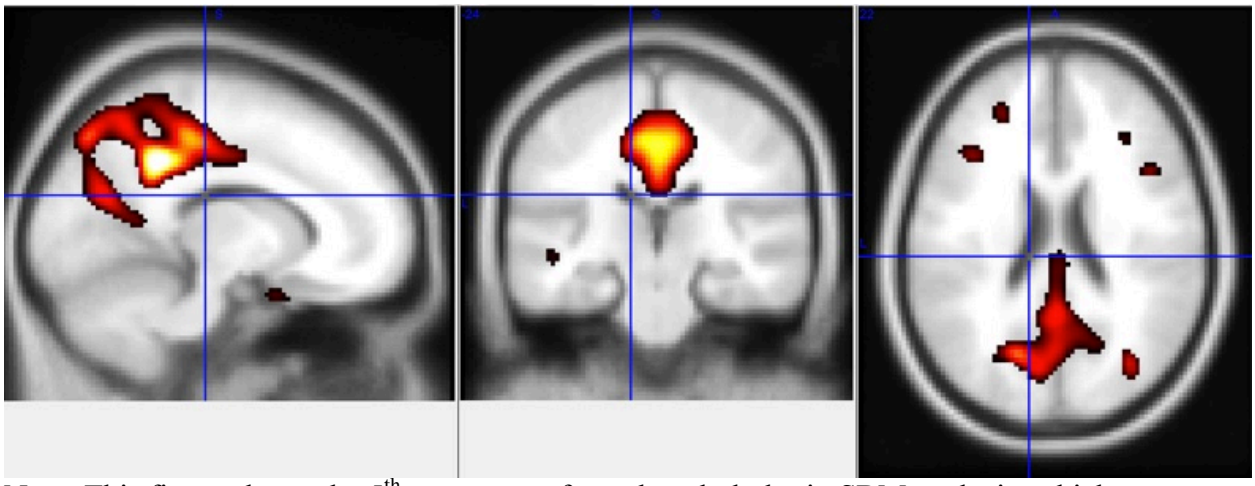
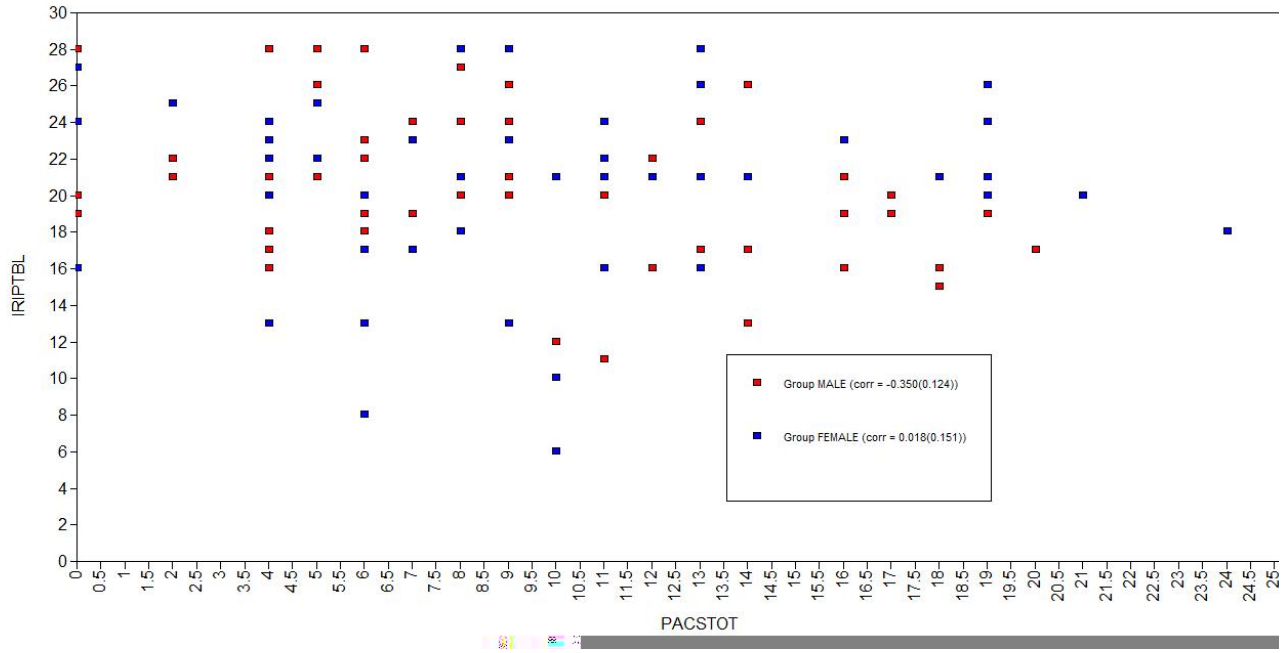


Figure 5—SBM Component 5



Note: This figure shows the 5th component from the whole-brain SBM analysis, which associated significantly with IRI PT across models.

Figure 6—Scatterplots for IRI PT with Total PACS for Men and Women



Note: This figure shows the simple slopes differences for men vs. women in the association between IRI Perspective Taking and alcohol craving on the PACS. There is an inverse association between IRI PT and total PACS for men (in red) but no association for women (in blue).

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