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ALTERATIONS IN RESTING STATE FUNCTIONAL CONNECTIVITY ASSOCIATED WITH ALCOHOL USE SEVERITY AND IMPULSIVITY IN A COMMUNITY SAMPLE

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ABSTRACT

Alcohol Use Disorder (AUD) is characterized by neurocognitive and behavioral impairments including the multidimensional construct of impulsivity. Increased impulsivity is both a risk factor for, and a consequence of problematic alcohol use. Individuals with AUD exhibit alterations in neural circuitry when compared to those who do not have AUD. These circuit-level changes in AUD may underlie the difficulties that these individuals experience with heightened impulsivity. The present study uses data-driven resting state functional connectivity (rsFC) methodology to examine the differences in intrinsic functional networks between individuals with AUD and those who are social drinkers (SD). Participants in this secondary data analysis were non-treatment seeking young adult alcohol drinkers (n = 53; with n = 23 who met criteria for an AUD). Group independent component analysis (gICA) was used to test AUD and SD group differences in within- and between-network rsFC, as well as associations between impulsivity constructs and these hypothesized alterations in rsFC. Although we expected to see hypoconnectivity in the AUD group, particularly among the default mode, executive control, reward, and salience networks, we found no statistically significant

group differences on any measure of rsFC. Furthermore, we found no associations between impulsivity constructs and rsFC in this sample. In order to explore these null findings, we visualized small-to-moderate effect size differences in spatial map intensity between the groups and found evidence for relatively reduced rsFC in frontal (orbitofrontal cortex, medial prefrontal, right frontal, anterior default mode), precuneus, and visual networks in AUD compared to SD. These effect sizes were small, representing statistically non-significant group differences in within-network rsFC, but they were in the expected direction of AUD hypoconnectivity. Given the statistically null findings, various explanations are presented and future directions are proposed to further advance our understanding of the associations between behavioral traits and neurobiological mechanisms that may contribute to risk for AUD among young adult drinkers.

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Introduction

Alcohol use is seen through multiple lenses in our society: it can be celebrated and enjoyed socially, yet it can also be associated with harmful consequences to the individual and to communities. Heavy alcohol use and alcohol use disorder (AUD) are associated with neurocognitive deficits, poorer physical and mental health outcomes, as well as substantial economic burden (de la Monte & Kril, 2014; Sacks, Gonzales, Bouchery, Tomedi, & Brewer, 2015). Social drinking is not consistently associated with neurocognitive deficits, although there is some limited evidence for certain executive function and reward system impairments (Crane et al., 2018; Montgomery, Fisk, Murphy, Ryland, & Hilton, 2012). Individuals with AUD show neurobiological deficits as compared to healthy controls, including structural, functional, and network level differences, which are associated with heightened impulsivity, decreased executive control, and increased reward-seeking (Koob & Volkow, 2016; Wilcox, Dekonenko, Mayer, Bogenschutz, & Turner, 2014). Examining functional connectivity patterns between social drinkers and those with AUD may help better characterize the neurobiological risk factors that underlie the behavioral deficits seen among individuals with AUD. Studying differences between those with AUD and those who drink alcohol socially without substantial consequences may improve prevention and treatment of AUDs by highlighting functional networks that represent either increased risk factors for AUD, or protective factors in social drinking.

Impulsivity

Operationalization of impulsivity. There is a strong association between AUDs and impulsivity, although specific relationships vary by study and by different

conceptualizations and assessments of impulsivity (Coskunpinar, Dir, & Cyders, 2013). Impulsivity is a multidimensional construct encompassing both personality traits and behavioral patterns (Dalley, Everitt, & Robbins, 2011; De Wit, 2009; Dick et al., 2010). It can be understood as the tendency to react quickly to internal or external stimuli, without consideration of potential consequences (Moeller, Barratt, Dougherty, Schmitz, & Swann, 2001). Whiteside, Lynam, and colleagues proposed a model to disentangle distinct aspects of impulsive personality traits using the five factor UPPS-P Impulsive Behavior Scale (Lynam, Smith, Cyders, Fischer, & Whiteside, 2007; Whiteside & Lynam, 2001). These five traits include: Lack of Planning (acting quickly, without careful planning), Sensation Seeking (favoring excitement and thrills), Lack of Perseverance (difficulty in seeing a task through to completion), Negative Urgency (tendency towards reckless actions during intense negative affect), and Positive Urgency (tendency towards reckless actions during intense positive affect). In fact, there is evidence to suggest that while some of these traits are related (e.g., lack of planning, lack of perseverance), others are distinct constructs entirely, sharing little variance with the other traits (e.g., urgency, sensation seeking) (G. T. Smith et al., 2007). Examining specific impulsivity constructs, rather than general impulsivity, is necessary in order to elucidate relationships between facets of impulsivity and specific drinking outcomes. In a recent meta-analysis of UPPS-P impulsivity traits and alcohol use, Coskunpinar and colleagues (2013) found that all five impulsivity traits equally predicted drinking frequency (medium effect sizes), lack of perseverance predicted drinking quantity (medium effect size), negative urgency and lack of planning strongly predicted AUD severity (approaching large effect size), and both negative and positive urgency were

strong predictors of alcohol-related consequences (approaching large effect size). These findings suggest that there may be distinct mechanisms underlying the associations between specific impulsivity traits and alcohol outcomes.

In addition to conceptualizations of impulsivity traits, there are distinct domains of impulsive behavior. Delay discounting tasks assess the tendency of an individual to choose smaller immediate rewards over larger delayered rewards. Greater delay discounting is commonly observed across addictive disorders (Bickel, Jarmolowicz, Mueller, Koffarnus, & Gatchalian, 2012). Another component of impulsivity is the extent to which one makes risky decisions that value reward without regard to potential consequences or losses. This type of impulsive behavior is typically assessed with tasks like the Iowa Gambling Task or the Balloon Analogue Risk Task, and those with addictive disorders tend to make more risky decisions in these tasks (Bechara, 2005; Fein & Chang, 2008). There are a variety of behavioral tasks that assess aspects of response inhibition, or the ability to stop an automatic response or a response that has already been initiated. These include Go-NoGo tasks, Stop-Signal tasks, and Continuous Performance tasks (Bari & Robbins, 2013) and there is strong evidence for poorer performance in these tasks among those with addiction (Dick et al., 2010; Stavro, Pelletier, & Potvin, 2013).

Furthermore, another construct related to impulsivity is impaired control. In the context of AUD, impaired control can be defined as difficulty following through on intentions to stop or limit alcohol use (Wardell, Quilty, & Hendershot, 2016). There are strong associations between impulsivity traits and impaired control even though they are unique constructs (Leeman, Patock-Peckham, & Potenza, 2012), and impaired control

may mediate the relationship between various domains of impulsivity and alcohol problems (Wardell et al., 2016). Therefore, impaired control is an important construct to consider when operationalizing and studying impulsivity.

Neural correlates of impulsivity. With numerous distinguishable impulsivity traits, there are also multiple neurobiological systems that subserve impulsive behavior. The amygdala and striatum are involved in attributing excessive affective salience and reward value to stimuli, leading to impulsive approach behavior in addictive disorders (Bechara, 2005). Disruptions in top-down executive control regions can also manifest in impulsive behavior. Classically, cortical regions including the anterior cingulate, dorsolateral prefrontal, orbitofrontal, and ventromedial prefrontal cortices are implicated in regulating (or failing to regulate) automatic responses in behavioral tasks such as the Go-NoGo (Bari & Robbins, 2013; Horn, Dolan, Elliott, Deakin, & Woodruff, 2003). These tasks specifically assess response inhibition, which is an aspect of motor impulsivity, or the tendency to take spur of the moment action (Moeller et al., 2001). Impulsive traits like lack of perseverance and lack of planning involve difficulty filtering out irrelevant information, a process which relies upon lateral orbitofrontal regions and the inferior frontal gyrus (Bechara, 2005). Given the complexity of the cortical and subcortical networks that underpin impulsive behavior, there is a clear need to precisely define the impulsivity construct of interest when studying the relationship between the brain's functional networks and behavior.

Impulsivity and addiction. The relationship between impulsivity and alcohol use is manifold (Dick et al., 2010). Increased impulsivity is both a risk factor for developing addictive behaviors (Verdejo-García, Lawrence, & Clark, 2008), as well as a result of

alcohol use (Wetherill, Squeglia, Yang, & Tapert, 2013). Greater trait impulsivity is associated with an earlier age of alcohol use onset, higher family density of AUD, binge drinking, and alcohol related problems in adolescence and young adulthood (Acheson, Vincent, Sorocco, & Lovallo, 2011; Lopez-Caneda, Rodríguez Holguín, Cadaveira, Corral, & Doallo, 2014; Martínez-Loredo et al., 2015). There is substantial behavioral and neurobiological evidence that addiction contributes to impaired executive control and heightened impulsivity, in conjunction with alterations in reward and motivational systems (Goldstein & Volkow, 2012; Lindgren et al., 2018). With more protracted substance use, individuals with alcohol and substance use disorders demonstrate difficulties with response inhibition, waiting, and in some cases risky-decision making, all of which correlate with different alterations in complex corticostriatal circuitry (Jentsch et al., 2014). A recent meta-analysis by Coskunpinar and Cyders suggests that there is also a link between substance-related attentional bias and behavioral impulsivity, rather than trait impulsivity (Coskunpinar & Cyders, 2013), which may be another underlying mechanism linking addiction and increased impulsivity. Given the evidence that distinct constructs of impulsivity are both risk factors for developing alcohol and other substance use disorders and consequences of substance use, precise study of underlying neurocognitive mechanisms may result in better prevention and treatment of alcohol and other substance use disorders.

Resting State Functional Connectivity in AUD

It is well documented that chronic and heavy alcohol use affects brain structure and function. Hallmark structural changes include reductions in cortical thickness in the superior frontal, precentral, postcentral, middle frontal, middle and superior temporal,

and lateral occipital gyri, degradation of cerebral white matter, and disruption of limbic circuitry (de la Monte & Kril, 2014). The degree of alcohol use severity is correlated with the extent of structural alterations (Fortier et al., 2011).

Recent literature on the long-term neuroadaptations resultant from alcohol use has focused on large scale functional networks that are associated with different aspects of addictive behavior (Koob & Volkow, 2010). Functional networks, or interconnected regions of the brain with temporally synchronous activity, illustrate how the brain works as an integrated unit to perform different types of tasks. Resting-state functional connectivity (rsFC) describes the brain's intrinsic circuitry made up of correlated and anti-correlated regions in the absence of any task (Biswal, Yetkin, Haughton, & Hyde, 1995). Even when not actively in use, resting state networks (RSNs) are strongly correlated with active functional networks, which makes studying rsFC an expedient way to detect the full array of functional brain networks (Mennes et al., 2010, 2011; Smith et al., 2009). The strength of networks at rest may predict subsequent fMRI task performance (Seeley et al., 2007) and correspond to various neuropsychiatric disease trajectories (Sutherland, McHugh, Pariyadath, & Stein, 2012).

Network level dysfunction provides a framework for understanding the complex cognitive and behavioral impairments seen in addiction (Lindgren et al., 2018). Various functional networks are altered in AUD relative to healthy controls, including default mode, executive control, reward, salience, attention and visual networks, although exact findings have been mixed between studies that vary in terms of rsFC analysis method, length of abstinence from alcohol, and other methodological differences. Specific deficits related to AUD have been found in interoceptive and sensory processing networks,

including salience, precuneous, sensorimotor, and visual networks; moreover, connectivity reduction between sensorimotor and visual areas is significantly related to scores on the Alcohol Use Disorders Identification Test (AUDIT) (Vergara, Liu, Claus, Hutchison, & Calhoun, 2017). Perhaps most closely involved in the construct of impulsivity is the executive control network, which appears to be altered in those with AUD who exhibit some expanded network connectivity among the superior frontal gyrus, medial frontal, right temporal, and cuneus/extrastriate cortical regions, as well as restricted connectivity with left parietal and inferior frontal regions (Müller-Oehring, Jung, Pfefferbaum, Sullivan, & Schulte, 2015). These executive control network rsFC differences in those with AUD correspond to poorer visuospatial working memory, slower perceptual-motor processing speed, higher mood and anxiety symptoms, as well as a younger age of alcohol use onset. Similarly, Weiland and colleagues (2015) found reductions in the strength of the left executive control network correlating with more severe impairments in controlling alcohol use and alcohol use severity. The brain network that is most active at rest, the default mode network, is less synchronized and less efficient in those with AUD (Chanraud, Pitel, Pfefferbaum, & Sullivan, 2011). However, during a working memory task, those with AUD, as compared to controls, exhibited greater connection strength among the posterior cingulate cortex (PCC, a key region in the default mode network) and other brain regions, even though the two groups did not differ on task performance. Additional rsFC network differences in those with AUD include findings from Müller-Oehring and colleagues (2015), who reported decreased salience network connectivity and extended frontostriatal connectivity in the reward network with less synchrony with limbic regions. These network alterations in

AUD can generally be understood in three ways: (1) network deficiencies, where weaker network connectivity is related to worse outcomes, (2) compensatory mechanisms, where stronger network connectivity is seen with normal task performance, and (3) network dedifferentiation, where stronger network connectivity relates to worse outcomes (Müller-Oehring et al., 2015).

Functional Connectivity and the Associations between Impulsivity and AUD

Although there is clear evidence for relationships between impulsivity and AUD, there is limited and conflicting research on the intrinsic functional networks that correspond with deficits in specific domains of impulsivity. As noted above, impulsivity is a multidimensional construct comprised of distinct personality traits and behavior patterns that are both risk factors for, and consequences of problematic alcohol use (Jentsch et al., 2014). Zhu and colleagues took a probabilistic independent component analysis (ICA) approach to compare within and between network connectivity among patients with alcohol dependence recruited from an inpatient treatment unit and healthy controls (Zhu, Cortes, Mathur, Tomasi, & Momenan, 2015). These rsFC findings were also correlated with three clinical measures of impulsivity: the Barratt Impulsiveness Scale (BIS-11), the UPPS-P Impulsivity Scale, and a delay discounting task. Among those with alcohol dependence, within-network connectivity of the amygdala–striatum network was negatively correlated with Negative Urgency, suggesting an overactive impulsive system that reacts to alcohol-cues and negative affective states that drive substance use. In addition, Zhu et al. found between-network connectivity among the left executive control network, salience network, and anterior default mode (a-DMN) networks was positively correlated with delay discounting, where this between-network

hyperconnectivity may be an example of network dedifferentiation (Müller-Oehring et al., 2015). Between-network connectivity among orbitofrontal cortex (OFC), left executive control network, and anterior default mode network, as well as OFC and posterior default mode network, were all negatively correlated with UPPS-P Negative Urgency, representing a network deficiency. In terms of overall group differences, these authors found participants with alcohol dependence had increased within-network functional connectivity in the salience network, default mode network, OFC, left executive control network and amygdala-striatum networks, as well as increased between-network functional connectivity among left executive control network, amygdala-striatum network, and salience network. This demonstrates a compensatory mechanism, where the brain of individuals with AUD must recruit additional resources in order to perform adequately.

This finding of increased intensity and breadth of rsFC in AUD seems to conflict with other findings in the literature. Overall, there are marked disruptions in within-network connectivity of the executive control network, default mode network (Zhu, Du, Kerich, Lohoff, & Momenan, 2018), as well as between sensory and motor networks (Vergara, Weiland, Hutchison, & Calhoun, 2017). Weiland and colleagues studied individuals with problematic alcohol use and found reduced connectivity in the left executive control network, which corresponded to more severe alcohol use and impaired control (Weiland et al., 2015). Vergara et al. also found a general pattern of hypoconnectivity, or reduced rsFC, among alcohol and nicotine users (Vergara, Liu, et al., 2017). At present, the only other study of impulsivity correlation with rsFC alterations in AUD comes from Wang and colleagues, who used a seed-based approach to

detect rsFC associations with the BIS-11, delay discounting task, Go-NoGo, and the Balloon Analogue Risk Task (BART) (Wang et al., 2016). Although these authors found that AUD participants had decreased rsFC between nodes in the reward network (mPFC, OFC, putamen, thalamus, parahippocampal gyrus) and higher scores on all impulsivity measures compared to healthy controls, there were no significant associations between specific rsFC alterations and impulsivity measures that survived correction for multiple comparisons. The BIS-11 is a measure of three impulsivity domains, attention impulsiveness, motor impulsiveness and non-planning impulsiveness. However, prior factor analytic research demonstrates that there may not be empirical support for these BIS subdomains (Reise, Moore, Sabb, Brown, Amira, & London, 2013), which may be one reason accounting for why prior studies by Zhu and colleagues (2015) and Wang and colleagues (2016) have not found any significant rsFC and impulsivity associations with this measure. Assessments that reliably differentiate specific domains of impulsivity and related aspects of behavioral control, such as the UPPS-P and ICS, are warranted. Furthermore, these groups present some conflicting findings on whether intrinsic rsFC of certain networks in AUD individuals is increased, suggesting compensatory mechanisms, or reduced, suggesting network deficiencies.

The task-based functional connectivity (FC) literature provides evidence for both network deficiencies and compensatory mechanisms, depending on specific task used. When non-treatment-seeking individuals with problematic alcohol use performed a Stop-Signal task, alcohol dependence severity was associated with weaker frontostriatal FC during response inhibition (Courtney, Ghahremani, & Ray, 2013). Yet on a Stroop task with emotion and alcohol cues, AUD participants performed equally well as control

participants but more robustly recruited reward circuitry and had greater midbrain-orbitofrontal cortical connectivity during alcohol trials than controls did, suggesting an overactive reward network biased towards alcohol cues (Müller-Oehring et al., 2013; Schulte, Müller-Oehring, Sullivan, & Pfefferbaum, 2012).

Various patterns of rsFC alterations can persist even after periods of abstinence from alcohol. Among recently abstinent patients with AUD, variation in rsFC was differentially associated with outcome, with weaker executive control, reward, and visual network connectivity predictive of relapse (Camchong, Stenger, & Fein, 2013). This indicates that while there are overall rsFC disruptions in AUD compared to healthy controls, specific differential rsFC patterns among drinkers may shed light on the mechanisms by which some individuals have more severe alcohol-related consequences than others.

Current Study

The goals of this secondary data analysis study were twofold: (1) to examine differences in resting state functional connectivity between individuals with alcohol use disorder (AUD) and social drinkers (SD), including both within- and between-network functional connectivity, and (2) to explore associations between rsFC alterations and distinct domains of impulsivity. By exploring the neural processes underlying impulsivity between two drinking groups, we may better characterize functional mechanisms that contribute to problematic versus non-problematic drinking.

There are two general analytical approaches in the rsFC literature (Li, Guo, Nie, Li, & Liu, 2009). Theory driven seed-based methods involve *a priori* hypotheses to inform the selection of regions of interest (ROIs) in order to test putative models when

there is strong neuroscientific backing. Seed-based methods assess correlations of BOLD (blood-oxygen-level dependent) signal time series between spatially distinct regions. Data-driven independent component analysis (ICA) instead assumes no prior model and has the ability to identify extensive functional connectivity networks. ICA involves decomposing the original BOLD time series into independent components (IC) and corresponding IC spatial maps that measure correlation. For this proposed study, data-driven ICA is the preferred analytical method given conflicts in the literature. Specifically, we used group ICA (gICA; Calhoun, Adali, Pearlson, & Pekar, 2001) in order to compare within- and between-network rsFC between our AUD and SD groups. In addition, RSNs identified by gICA may be differentially associated with multidimensional impulsive personality traits.

Hypotheses

Given evidence in the literature for a general "hypoconnectivity syndrome" (Vergara, Liu, et al., 2017), we hypothesized that (1) AUD participants will show reductions in within-network resting connectivity in the default mode, executive control, reward, and salience networks compared to SD. We also hypothesized that (2) AUD participants will demonstrate altered between-network connectivity patterns compared to SD. In addition, we expected that (3) AUD group rsFC alterations will be associated with increased impulsivity traits.

Method

Participants

Social drinkers (SD; *n*=30) and individuals with alcohol use disorder (AUD; *n*=23) were recruited from the community. Social drinkers consumed alcohol at least

once over the four weeks prior to enrollment and reported drinking levels that did not surpass National Institute on Alcohol Abuse and Alcoholism (NIAAA) criteria for low-risk drinking (i.e., no more than 3/4 drinks per day, or 7/14 drinks per week for women/men). In addition, social drinkers did not meet criteria for any current or lifetime alcohol use disorder. The AUD group was comprised of individuals who met criteria for current alcohol dependence or alcohol abuse per the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR; American Psychiatric Association, 2000) criteria, reported at least five binge drinking episodes (3+/4+ drinks for women/men) during the four weeks prior to enrollment, had no history of treatment for AUD or current desire for treatment, and no history of severe alcohol withdrawal. All participants were between the ages of 21-30, right-handed, and had no MRI contraindications, no history of neurological injury, or other current or lifetime substance use disorder besides alcohol, nicotine, or cannabis.

Measures

Demographics. A brief demographics questionnaire was used to obtain information such as age, ethnicity, socioeconomic status, and education.

Alcohol Use Severity. The Alcohol Use Disorder Identification Test (AUDIT; Saunders, Aasland, Babor, De La Fuente, & Grant, 1993) was used to determine eligibility and assess hazardous drinking. The Structured Clinical Interview for DSM-IV Disorders (SCID-IV; First, Williams, Spitzer, & Gibbon, 2002) was administered to determine current and lifetime diagnoses of alcohol dependence or alcohol abuse. Past 90-day quantity and frequency of drinking was assessed using the Timeline Follow-Back (TLFB; Sobell & Sobell, 1996).

Impulsivity and Behavioral Control. The UPPS-P Impulsive Behavior Scale (Lynam, Smith, Cyders, Fisher, & Whiteside, 2007) is a revised version of the original UPPS Scale (Whiteside & Lynam, 2001). It is a 59-item measure on a four point Likert scale designed to assess five impulsivity-related traits, including Lack of Planning (11 items), Lack of Perseverance (10 items), Sensation Seeking (12 items), Negative Urgency (12 items), and Positive Urgency (14 items). The Impaired Control Scale (ICS; Heather, Booth, & Luce, 1998) includes 25 items related to whether individuals have attempted to, failed to, or perceived that they can control their drinking behavior. The UPPS-P and the ICS both demonstrated good internal consistency in this sample, with Cronbach's alpha of .94 and .82, respectively.

Image Acquisition

Functional and anatomical MRI data was acquired via a 3T Siemens Trio whole-body scanner equipped with a 32-channel head coil. Participants were placed in the scanner and a piece of tape was placed across the participant's forehead to serve as feedback to reduce head movement. The scan sequence was as follows: localizer scans, several functional runs using an echo-planar (acceleration factor=8) gradient pulse sequence [repetition time (TR)=460ms, echo time (TE) = 29, flip angle = 44°]. Images were acquired parallel to the ventral surface of a participants' orbitofrontal cortex to reduce signal dropout and distortion in this region (Deichmann, Gottfried, Hutton, & Turner, 2003). Each volume consisted of 56 axial slices (64x64 matrix, 3.02 x 3.02 mm^2, 3.00-mm thickness, no gap). The resting state scan was the first functional scan of the scanning session and was five minutes in duration. Additionally, a high-resolution multi-echo T1-weighted magnetization-prepared rapid acquisition with gradient echo (MP-

RAGE) anatomical image was acquired (TR=2,530ms, TE=1.64, 3.5, 5.36, 7.22, and 9.08 ms, flip-angle=7°, 192 sagittal slices, 256x256 matrix, 1.0 x 1.0 mm^2, slice thickness=1-mm, no gap).

Data Analysis

Debiased images were pre-processed using Statistical Parametric Mapping 12 software (SPM; http://www.fil.ion.ucl.ac.uk/spm) (Friston, 2003). Preprocessing steps included realignment, normalization, regression of motion parameters, detrending, and smoothing. The first 10 of the 650 volumes were discarded to remove T1 equilibration effects. Images were realigned with the INRIAlign toolbox (Freire, Roche, & Mangin, 2002) using the default cut-off of 2.5. EPI images were normalized to the MNI152 template in SPM12. Regression of motion parameters from the normalized timeseries included spikes, linear, quadratic, and cubic trends, six motion parameters, and realignment parameter derivatives (Vergara, Mayer, Damaraju, Hutchison, & Calhoun, 2017). Images were smoothed using a Gaussian smoothing kernel ($6mm^3$).

These preprocessed data were then analyzed with Infomax-based spatial GIG-ICA (Du et al., 2016) with ICASSO (Himberg, Hyva, & Esposito, 2004; Ma et al., 2011) using variance normalization and Z score scaling in the group ICA of fMRI toolbox for Matlab (GIFT; Calhoun, 2004). Standard principal components analysis was run with two data reduction steps.

In terms of determining an optimal number of independent components, there are two trends in the field: higher order analyses generate more focal networks, while lower order analyses produce larger networks (Calhoun & de Lacy, 2017). Although these two approaches both ultimately show the same signal decomposed into more or less specific

networks, there are some slight benefits to each approach and thus we conducted both a low order and a high order ICA. For the low order, we conducted GIG-ICA with 27 and 20 components for the first and second decomposition levels. For the high order, we used 100 and 75 components for the first and second decomposition levels. Components representing true BOLD signal were independently identified from each ICA by visual inspection by two authors. Discrepancies were then discussed and reconciled.

Functional Connectivity Analysis

To test all dependent variables in this study, we used the Mancovan toolbox in GIFT, which allows for the analysis of covariance of three aspects of functional connectivity: power spectra of RSN time courses, RSN spatial map intensities, and functional network connectivity (FNC) between RSNs (Allen et al., 2011). Power spectra of RSN time courses refers to the level of coherence of BOLD activity within a given component, while RSN spatial map intensity refers to the intensity of voxels contributing to a given component, thresholded with a voxelwise *t*-statistic. FNC between RSNs describes the correlation between each pair of ICs in the analysis, a measure between-network connectivity.

For the primary hypothesis of this study that AUD participants would show reductions in within-network resting connectivity in the default mode, executive control, reward, and salience networks compared to SD, MANCOVAs were run to assess group differences on the RSN spatial maps of identified components between AUD and SD groups for the high and low order ICAs. To test the second hypothesis about between-network connectivity differences in AUD compared to SD, we used the Mancovan toolbox to examine the correlations among RSNs between these groups. To test the third

hypothesis about associations with rsFC alterations and impulsivity, additional MANCOVAs were conducted with impulsivity variables of interest based on previous literature demonstrating the association between negative urgency with alcohol related problems, negative urgency and lack of planning with alcohol dependence severity, as well as failed control with alcohol dependence severity and consumption (Coskunpinar et al., 2013; Marsh, Smith, Saunders, & Piek, 2002). Specifically, separate MANCOVAs were run testing the following covariates: Negative Urgency (UPPS-P subscale), Lack of Planning (UPPS-P subscale), and Failed Control (ICS subscale). Statistical significance for each MANCOVA was assessed with an alpha threshold of $p<.01$, corrected for multiple comparisons.

Power analysis. We conducted a power analysis in G*Power 3.1 (Faul, Erdfelder, Buchner, & Lang, 2009; Faul, Erdfelder, Lang, & Buchner, 2007) using our group sizes (AUD n=23; SD n=30), desired power >0.80, and a two-tailed $\alpha<0.05$, revealing that we will have adequate power to detect an effect size of d=0.70 in within- and between-network correlation analyses with UPPS-P impulsivity subscales. Prior research by Zhu and colleagues (2016) identified large effect sizes (Cohen's $d > 1.19$) in ICA analyses of within- and between-network correlational analyses with the UPPS-P in AUD participants as compared to healthy controls, with correlations ranging from $r = -0.51$ (UPPS-P with OFC*executive control network) to $r = -0.58$ (UPPS-P with OFC*anterior default mode network). Thus, the current study was sufficiently powered to detect large effect size associations in within- and between-network correlation analyses.

Results

Descriptive Statistics

The sample was 56.6% female and mostly Hispanic (35.4%) or non-Hispanic White (64.6%). Average age was 24.0 (SD= 2.6). Average AUDIT scores in the AUD group was 11.61 (SD=5.57), which was significantly higher than the average AUDIT scores in the SD group (Mean=5.00, SD=2.08; t (51) = 5.41, $p < 0.01$). Individuals in the AUD group also had significantly more AUD symptoms (t (51) 9.34, $p < 0.01$) and reported greater perceived failed control over alcohol use (t (51) 2.72, $p = 0.02$). The groups did not differ from one another on any of the UPPS-P impulsivity measures. See Table 1 for additional demographic information by the AUD and SD groups and Table 2 for group alcohol and impulsivity characteristics.

Functional Connectivity Analysis

We identified independent components (ICs) that captured true BOLD signal from the low order and high order group ICA analyses based on visual inspection and low frequency to high frequency power ratio consistent with BOLD signal, rather than other artifacts. From the low order GIG-ICA, 11 out of the 20 estimated components were selected as resting state networks of interest. For the high order GIG-ICA, 27 out of the 75 estimated components were selected. These 11 and 27 components, respectively, were identified because they appeared to have low noise and to be largely free of artifacts based on visual inspection and low to high frequency power ratio. Components were independently identified by two authors and a small number of discrepancies were discussed and reconciled. In both the low and high order ICAs, these ICs corresponded to widely replicated regions that comprise RSNs found by previous researchers, suggesting

that they represent fundamental components of human brain connectivity. These ICs are shown in Figures 1 and 2, and coordinates presented in Tables 3 and 4 for the low order ICA and high order ICA, respectively.

Test of Hypotheses 1 and 2: Association between rsFC and AUD.

MANCOVA revealed no significant AUD/SD group differences in power spectra of RSN time courses, RSN spatial map intensities, or FNC on any IC of interest from the low or high order ICA. In order to examine these statistically insignificant results further, effect size maps were rendered to visualize RSN spatial map intensity differences between AUD>SD and SD>AUD contrasts for the identified ICs from the low (Figure 3) and high (Figure 4) order gICAs.

Given the main analyses were only powered to detect effect sizes greater than 0.7, we estimated effect size maps that were thresholded to display spatial map intensity differences between small and moderate effect sizes (Cohen's d = 0.3 - 0.7). Overall, these effect size maps demonstrate several small increases in connectivity in SD compared to AUD, one instance of increased connectivity in AUD compared to SD, and some inconclusive findings of effects in both directions (AUD>SD and SD>AUD) within the same network. Specifically, from the low order gICA we see small effects in IC 5, anterior default mode network, with SD exhibiting greater connectivity in bilateral frontal cortical regions. In IC 7, the right executive network, we see slight increases in AUD connectivity over SD in right parietal regions. In addition, the effect size map of IC 14, salience network, shows that the SD group has greater connectivity in the orbitofrontal cortex than AUD, but there is also evidence of adjacent cortical regions showing the opposite pattern of connectivity (AUD>SD). From the high order gICA, the SD group

demonstrated small increases in connectivity over AUD in medial prefrontal cortex (IC 36), visual cortex (IC 40), precuneus (IC 64), and right frontal cortex (IC 67). Several networks included inconclusive findings of adjacent regions with mixed AUD>SD and SD>AUD connectivity, including the anterior cingulate cortex (IC 53), and left frontal cortex (IC 68). Taken together, the low and high order gICA effect size maps show some limited support for SD having relatively stronger rsFC in frontal areas (orbitofrontal cortex, medial prefrontal, right frontal, anterior default mode), precuneus, and visual regions, but an unexpected finding of relatively stronger rsFC in the AUD group in parietal regions. These effect sizes are small, representing statistically non-significant group differences in within-network rsFC.

Test of Hypothesis 3: Associations between rsFC and Impulsivity. Analyses were conducted testing the association of the identified IC sets with the primary impulsivity construct variables: negative urgency (UPPS-P), lack of planning (UPPS-P), and failed control (ICS). MANCOVA revealed no significant associations between any of these impulsivity construct variables and the power spectra of RSN time courses, RSN spatial map intensities, or FNC on any IC of interest from the low or high order ICA.

Exploratory Analysis: Controlling for AUD Severity. Because we did not find evidence for statistically significant AUD/SD group differences in rsFC, nor associations with impulsivity and rsFC, we conducted exploratory MANCOVA analyses with the low and high order ICs to probe for possible explanations of null findings. The first exploratory MANCOVA we conducted included the number of DSM-IV AUD diagnostic criteria as a covariate because we hypothesized that this would be a more sensitive measure of alcohol use severity than the AUD/SD group test because it would

approximate the DSM-5 spectrum of severity in AUD (Hasin et al., 2013). The AUD/SD participants in this study were classified, in part, based on the presence or absence of DSM-IV alcohol abuse or alcohol dependence. In actuality, some members of the SD group endorsed one or two criteria for an AUD, but were "diagnostic orphans" since they did not meet threshold for abuse or dependence, while some members of the AUD group also endorsed one or two criteria, but did meet for a diagnosis. We hypothesized that this first exploratory MANCOVA with number of DSM-IV AUD criteria as a covariate would better capture the spectrum of alcohol use severity within whole sample. However, there were no statistically significant associations between number of DSM-IV AUD criteria and the power spectra of RSN time courses, RSN spatial map intensities, or FNC on any IC of interest from the low or high order ICA.

Exploratory Analysis: Differences by Gender. Second, we revisited prior literature demonstrating that males exhibit greater sensation seeking, another construct of impulsivity not originally tested in this study, but the relationship between sensation seeking and alcohol use outcomes in invariant across genders in non-clinical samples (Cyders, 2013). In this study, we probed the data and found evidence of a weak interaction between UPPS-P sensation seeking and sex predicting alcohol use disorder severity, such that number of DSM-IV AUD criteria was positively associated with sensation seeking for men (r = .39, p = .07), but not for women (r = -.05, p =.79), so we included UPPS-P sensation seeking and sex as covariates in a second exploratory MANCOVA. We found no statistically significant associations between number of DSM-IV AUD criteria, sex, or their interaction and the power spectra of RSN time courses,

RSN spatial map intensities, or FNC on any IC of interest from the low or high order ICA.

Exploratory Analysis: Controlling for Failed Control. Finally, we ran a MANCOVA with failed control (ICS subscale) and AUD/SD group as covariates. Previous literature has indicated that impaired control over alcohol is a distinct but important construct in understanding the relationship between impulsivity and alcohol use outcomes among individuals with differential risk for AUD (Wardell, Quilty, & Hendershot, 2015). In this sample, failed control was the only impulsivity-related construct that was significantly different between AUD and SD (F (1,51) = 7.41; p = .009). We found no statistically significant association between the interaction between failed control and AUD/SD group and the power spectra of RSN time courses, RSN spatial map intensities, or FNC on any IC of interest from the low or high order ICA.

Discussion

The overarching aim of this study was to compare resting state functional connectivity (rsFC) between those with alcohol use disorder (AUD) and those who are social drinkers (SD). Although there has been previous research on the alterations of brain functional networks in AUD, further clarification has been warranted in order to describe these neural alterations as they relate to relevant behavioral outcomes as either network deficiencies, compensatory mechanisms, or dedifferentiation of functional networks. In the current study, we set out to characterize within-network functional connectivity, between-network functional connectivity, and associations of those connectivity patterns with impulsivity constructs. Using both a low order and a high order group ICA, we identified well-established large scale functional networks in the brain

(e.g., default mode, sensorimotor, executive control networks). This suggests that our data-driven analysis method was adequate to characterize major functional networks.

Contrary to hypotheses based on previous literature (Chanraud et al., 2011; Courtney et al., 2013; Müller-Oehring et al., 2015; Vergara, Liu, et al., 2017; Vergara, Weiland, et al., 2017; Wang et al., 2016; Weiland et al., 2015), we did not find evidence for a marked pattern of hypoconnectivity among those with AUD. First, we compared the BOLD signal of identified components between AUD and SD and found no statistically significant differences in activation between groups. Upon examining effect size maps visualizing small-to-medium effects between AUD and SD spatial map intensities, we did find evidence in SD for minor increases in within-network rsFC in frontal areas (orbitofrontal cortex, medial prefrontal, right frontal, anterior default mode), precuneus, and visual regions. However, we also found an unexpected result of relatively stronger rsFC in the AUD group in parietal regions. Although most of these effects were in the hypothesized direction, none of these group comparisons rose to the level of statistical significance. We also compared functional network connectivity, or the extent to which distinct ICs co-activate with one another, and again found no statistically significant difference between the AUD and SD groups. Given these unexpected null findings, we tested an exploratory hypothesis that using a continuous measure of alcohol use severity might be more sensitive to the functional connectivity alterations associated with alcohol use. To this end, we conducted a MANCOVA to assess the relationship between number of DSM-IV AUD criteria and within- and between-network functional connectivity. This analysis method better reflects the evolution of the AUD diagnosis in the DSM-5 toward a spectrum of severity, rather than broader, binary diagnostic categories (Hasin et al.,

2013). Nonetheless, we found no statistically significant associations between number of DSM-IV AUD criteria and activation of ICs or functional network connectivity between ICs.

There is an extensive literature on the role of impulsivity as both a risk factor for, and consequence of problematic alcohol use. Often inconsistently specified in the literature, impulsivity is a heterogeneous construct that encompasses various and distinct personality traits and behavioral patterns (Dalley et al., 2011; De Wit, 2009; Dick et al., 2010; Whiteside & Lynam, 2001). Because specific constructs within impulsivity have been linked to different alcohol related outcomes and neural characteristics, we tested the associations of three previously validated variables (Coskunpinar et al., 2013): negative urgency, lack of planning, and failed control with functional connectivity in this sample. No significant associations were found between these impulsivity variables and within- or between-network functional connectivity.

Following these unexpected null findings, we probed the data in an effort to understand the role of impulsivity characteristics in our sample, and tested two exploratory hypotheses. First, consistent with prior studies demonstrating that men report higher sensation seeking than women (Cyders, 2013), we found an interaction between sensation seeking and sex, such that sensation seeking was positively associated with alcohol use disorder severity among men only. Thus, we tested the effect of sensation seeking and sex on functional networks. Again, we found no significant impact of sensation seeking or sex or the interaction on within- or between-network functional connectivity. In addition, given research on the association between AUD and impaired control (Leeman et al., 2012; Wardell et al., 2016), we examined the relationship between

functional networks and failed control, with AUD/SD group membership as a covariate. Again, we found no significant association between failed control and AUD/SD group on any functional connectivity measure.

There are several possible factors that could account for the lack of significant relationships in this study between brain functional networks and alcohol use severity or impulsivity. Much of the previous literature in this area has focused on more severe AUD groups than the one used in this study. For example, a study by Müller-Oehring and colleagues found various alterations in within- and between network connectivity in an AUD group compared to healthy controls. Their AUD group scored substantially higher on the Alcohol Use Disorders Identification Test (AUDIT) than the AUD group of the current study did (M = 26.6 compared to M = 11.6), met for multiple other substance use disorders (35% Cocaine Use Disorder), and were recruited from treatment settings; all of these factors indicate a more severe sample (Müller-Oehring et al., 2015). Other researchers who have found patterns of hypoconnectivity in the brains of individuals with AUD have also reported higher AUDIT scores from their AUD groups (Vergara, Liu, et al., 2017; Weiland et al., 2015), and have recruited participants from inpatient treatment settings (Wang et al., 2016; Zhu et al., 2015). In the AUD sample used in this study, only 17% of participants met six or more DSM-IV AUD criteria, approximately equivalent to DSM-5 AUD severe. Because the current study compared a relatively less severe AUD group to a social drinking group, the magnitude of difference between these groups may have been too low to detect smaller functional connectivity effects. Due to the cross-sectional design of this study, we were unable to determine whether the lack of large functional connectivity differences between groups was caused by the lack of alcohol-

related impacts on the brain (e.g., the AUD group had not been drinking long enough or severely enough to develop neural changes), or the lack of underlying neural vulnerabilities (e.g., the AUD group was less severe because they had relatively more neuroprotective factors to begin with).

Similarly, it is notable that we found no statistically significant difference between the AUD and SD groups on negative urgency, lack of planning, or sensation seeking. Meta-analyses have shown that these three facets of impulsivity are associated with alcohol related problems, dependence severity, and binge drinking, respectively (Coskunpinar et al., 2013). Although our AUD group did report significantly higher failed control over alcohol use than the SD group, their failed control scores were lower than other comparable AUD samples (M= 12. 6 compared to M = 16.8; Weiland et al., 2015). In addition to demonstrating lower alcohol use severity, the sample in this current study also reported less impulsivity than typical AUD samples in the extant literature. Although we found evidence in the effect size maps for small reductions in within-network rsFC in frontal (orbitofrontal cortex, medial prefrontal, right frontal, anterior default mode), precuneus, and visual networks in AUD compared to SD, this relatively small pattern of hypoconnectivity did not correspond to any impairments in self-reported impulsivity in the AUD group. Thus, although there may be some alterations in AUD rsFC, these alterations do not represent network deficiencies.

The current study is not without limitations. Given that this sample represented less severe alcohol use and impulsivity characteristics than is typical for AUD samples in the literature, there may have been small to medium effects that this study was underpowered to detect in statistical analyses. This study was only powered to detect

moderately large effect sizes. Furthermore, we only included self-report measures of impulsivity. Although these impulsivity assessments have been previously validated in alcohol using populations, it is possible that a behavioral measure of impulsivity could have better distinguished differences in impulsivity between the AUD and SD groups in this sample. In addition, the cross-sectional design of this study may have limited the findings. It is likely that among the AUD group, some participants would have eventually sought treatment for their alcohol use, while others may have resolved their problematic alcohol use on their own (Witkiewitz, Dearing, & Maisto, 2014). Following a young adult AUD group over time could reveal alcohol use trajectories that are associated with certain characteristics of resting state functional networks. Lastly, the conclusions drawn from this study may not generalize to the AUD population as a whole. Rather, the findings should be applied only to non-treatment-seeking young adults with moderate AUD, as this may be a relatively less severe AUD sample with some distinct characteristics from their more severe counterparts.

Out of the unexpected findings from this study come future directions to clarify the discrepancies within the AUD and resting state functional connectivity literature. Previous research has demonstrated a fairly consistent pattern of hypoconnectivity within brain functional networks, as well as disrupted between network connectivity. However, these functional connectivity alterations have not always been adequately characterized in the context of the behavioral correlates that they subserve. In this study, we found evidence for marginal within-network rsFC reductions in the AUD group in frontal areas (orbitofrontal cortex, medial prefrontal, right frontal, anterior default mode), precuneus, and visual regions, yet the AUD group did not show any impairments in impulsivity

constructs that might be influenced by these functional networks including negative urgency, lack of planning, or sensation seeking. Unlike previous AUD rsFC research that has recruited more severe AUD samples with clear impulsive traits, the slight reductions in rsFC in this study do not reflect network deficiencies because these alterations do not correspond to differences in impulsive traits or behavior.

The findings of this study imply that there may be subgroups of the AUD population that, while they have some alcohol-related consequences, do not necessarily experience the behavioral difficulties that typically accompany more severe AUDs. Due to the cross-sectional design of this study, we were not able to determine whether these mild rsFC alterations seen here represent an earlier stage in AUD progression such that the alterations would become more pronounced over time, or rather, if mild rsFC alterations with no behavioral correlates instead predict those who are more likely to self-change their drinking over time.

Future research in this area would benefit from continuing to specify the behavioral traits or vulnerabilities that come along with certain neural connectivity patterns. It would be valuable to study the ways in which rsFC varies among those with AUD, as well as between individuals with AUD and those who are social drinkers in order to more fully characterize rsFC alterations as network deficiencies (reduced connectivity and poorer behavioral outcome), compensatory mechanisms (increased activation to achieve normal outcome), or as evidence of network dedifferentiation (increased activation within- and between-networks associated with poorer outcome).

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Table 1

Demographics

	Alcohol Use Disorder (n=23)	Social Drinkers (n=30)
	N(%) / M(SD)	N(%) / M(SD)
Gender		
Female	13 (56.5%)	17 (56.7%)
Male	10 (43.5%)	13 (43.3%)
Race/Ethnicity		
Hispanic or Latina/Latino	9 (39.1%)	8 (26.7%)
Non-Hispanic White	8 (34.8%)	14 (46.7%)
Asian	1 (4.3%)	0 (0.0%)
American Indian/Alaska Native	2 (8.7%)	0 (0.0%)
More than one race/ethnicity	1 (4.3%)	2 (6.7%)
Native Hawaiian/Pacific Islander	1 (4.3%)	0 (0.0%)
Unknown or not reported	1 (4.3%)	6 (20.0%)
Age	23.7 (2.7)	24.3 (2.6)
Employment		
Full time job	3 (13.0%)	6 (20.0%)
Full time student	11 (47.8%)	13 (43.3%)
Part-time, odd jobs	6 (26.1%)	9 (30.0%)
Unemployed or disabled	3 (13.0%)	2 (6.7%)
Education		
High school diploma/GED	3 (13.0%)	2 (6.7%)
Some college	10 (43.5%)	9 (30.0%)
Associates or technical	3 (13.0%)	5 (16.7%)
Bachelor's degree	7 (30.4%)	13 (43.3%)
Master's degree	0 (0.0%)	1 (3.3%)
Household Income		
$0 - $19,999/year	12 (52.2%)	11 (36.7%)
$20,000 - $39,999/year	9 (39.1%)	8 (26.7%)
$40,000 - $59,999/year	2 (8.7%)	7 (23.3%)
Over $60,000/year	0 (0.0%)	4 (13.3%)
Marital Status		
Never married	18 (78.3%)	24 (80.0%)
Married or living together	4 (17.4%)	4 (13.3%)
Separated	1 (4.3%)	2 (6.7%)

Note: Chi-Square and *t*-tests indicate none of these demographics were significantly different between groups.

Table 2

Alcohol use characteristics

	Alcohol Use Disorder	Social Drinkers
	M(SD)	M(SD)
AUDIT	11.61 (5.57)**	5.00 (2.08)**
DSM-IV AUD criteria	4.65 (2.27)**	0.17 (0.46)**
UPPS-P		
Negative Urgency	2.12 (0.53)	1.97 (0.63)
Lack of Planning	1.94 (0.55)	1.80 (0.41)
Sensation Seeking	3.01 (0.65)	2.92 (0.49)
ICS		
Failed Control	12.61 (10.18)*	6.67 (5.52)*
Age of alcohol use onset	15.45 (2.50)	16.50 (2.69)

Note: * *t*-test p<0.01. ** *t*-test p<0.001. AUDIT = Alcohol Use Disorder Identification Test. DSM-IV AUD criteria = number of diagnostic criteria endorsed on the SCID. UPPS-P = UPPS-P Impulsive Behavior Scale. ICS = Impaired Control Scale.

Table 3

Low order gICA

RSN	IC	Brain Region	MNI-X	MNI-Y	MNI-Z
Basal Ganglia	3	Left Pallidum	-12	2	-2
Sensorimotor	4	Precentral Gyrus	18	-24	60
Anterior Default Mode	5	Frontal Pole	-6	62	28
Auditory	6	Central Opercular Cortex	-54	-16	14
Right Executive Control	7	Frontal Pole	42	54	-4
Default Mode	11	Posterior Cingulate Gyrus	0	-30	26
Sensorimotor	13	Postcentral Gyrus	-60	-26	44
Salience	14	Orbital Frontal Cortex	42	22	-10
Left Executive	16	Frontal Pole	-48	42	-8
Visual	17	Supracalcarine Cortex	4	-80	8
Visual	18	Inferior Lateral Occipital Cortex	-42	-82	-4

Table 4

High order gICA

RSN	IC	Brain Region	MNI-X	MNI-Y	MNI-Z
Sensorimotor	17	Postcentral Gyrus	-56	-8	25
Sensorimotor	20	Precentral Gyrus	4	-28	65
Cerebellum	28	Right Cerebellum	34	-76	-35
Default Mode	29	Right Hippocampus	36	-32	-10
Right Executive	33	Inferior Frontal Gyrus	42	24	10
Sensorimotor	35	Postcentral Gyrus	-44	-28	60
Anterior Default Mode	36	Frontal Pole	-6	58	35
Visual	40	Lateral Occipital Cortex	-36	-66	0
Sensorimotor	46	Supplementary Motor Cortex	-6	2	60
Visual	49	Supracalcarine Cortex	0	-82	10
Sensorimotor	50	Precentral Gyrus	30	-22	45
Default Mode	52	Posterior Cingulate Gyrus	-8	-28	25
Salience	53	Anterior Cingulate Gyrus	-6	14	25
Visual	59	Occipital Pole	22	-92	-10
Attention	61	Supramarginal Gyrus	-46	-50	15
Default Mode	64	Precuneous Cortex	8	-58	65
Auditory Network	65	Heschl's Gyrus	-36	-28	5
Visual Network	66	Middle Temporal Gyrus	48	-40	-5
Right Executive	67	Middle Frontal Gyrus	26	32	35
Left Executive	68	Frontal Pole	-34	52	15
Attention	69	Middle Frontal Gyrus	-32	6	35

Attention	70	Posterior Middle Temporal Gyrus	-46	-40	-5
Visual	71	Inferior Lateral Occipital Cortex	38	-72	0
Default Mode	72	Posterior Cingulate Gyrus	8	-50	10
Default Mode	73	Precuneous Cortex	2	-64	35
Left Executive	74	Frontal Operculum Cortex	-42	22	5
Auditory	75	Planum Temporale	36	-28	15

Figure 1. Low order gICA independent components of interest

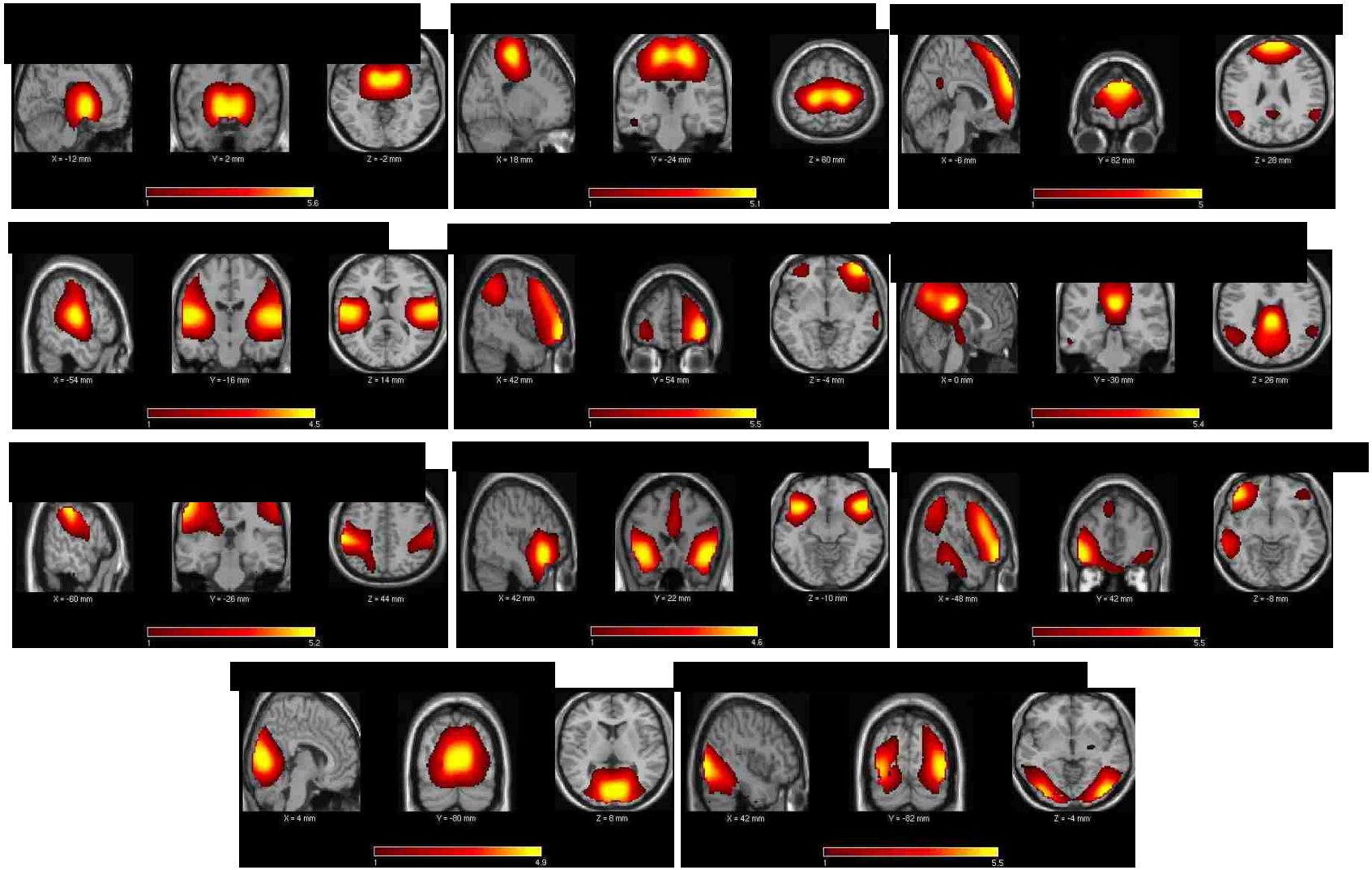
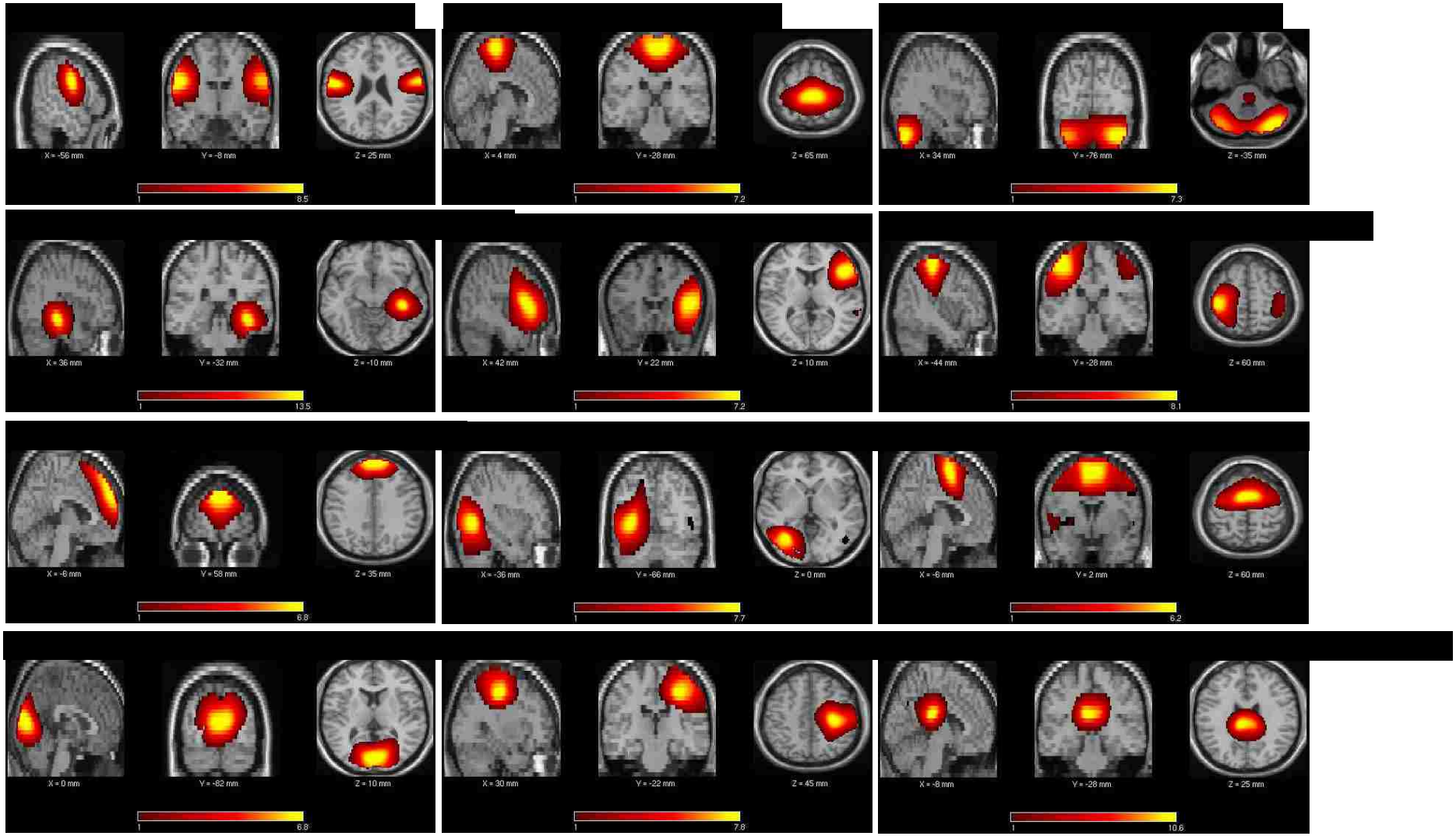


Figure 2. High order gICA components of interest



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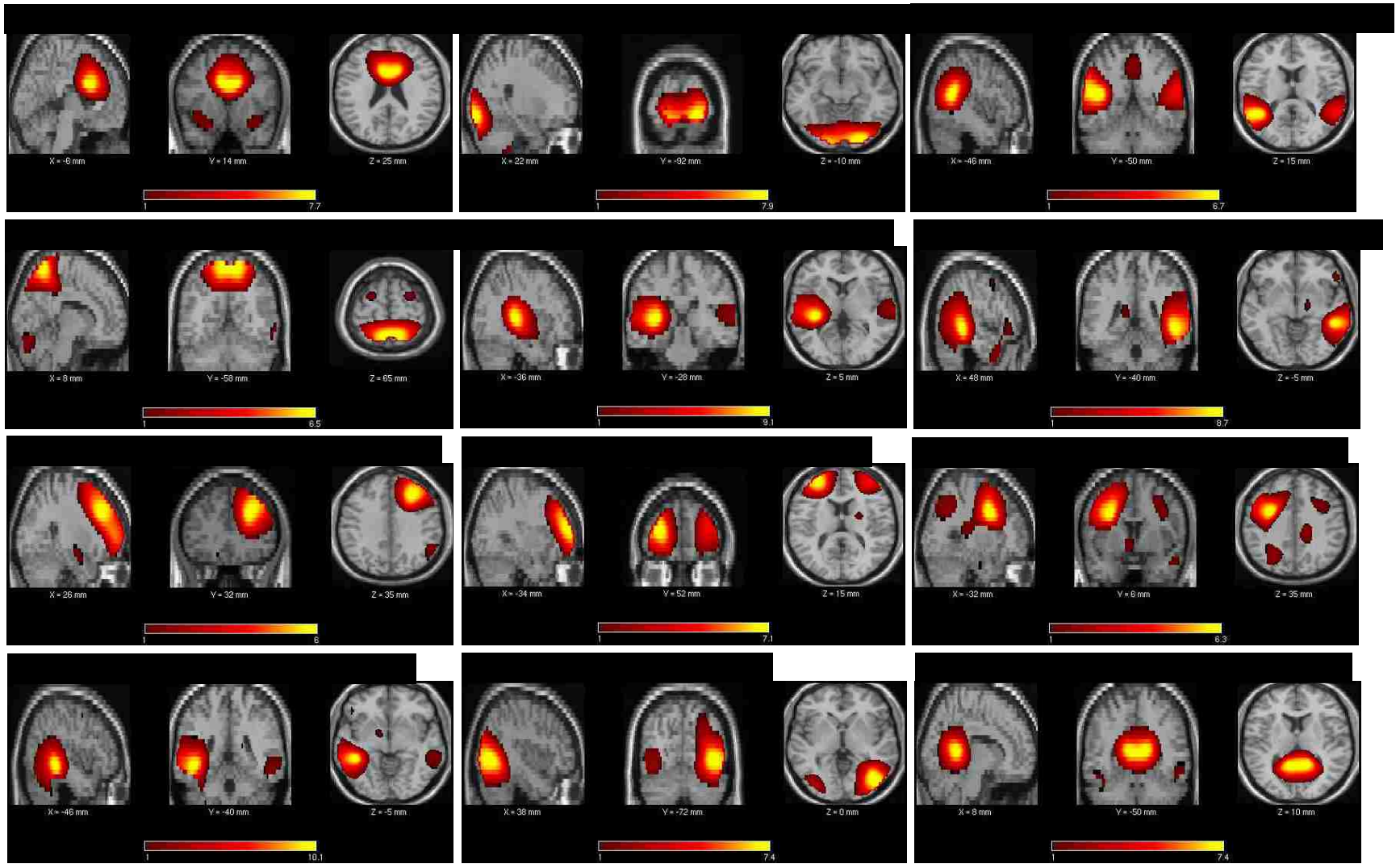

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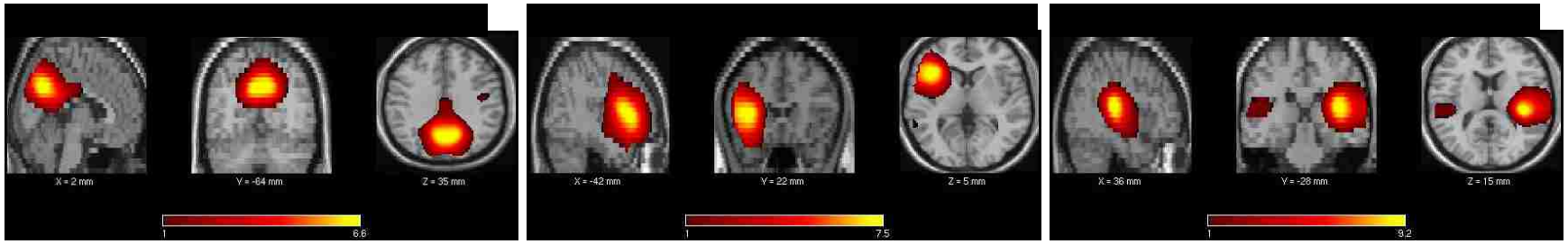


Figure 3. Low order effect size maps with AUD>SD and SD>AUD contrasts

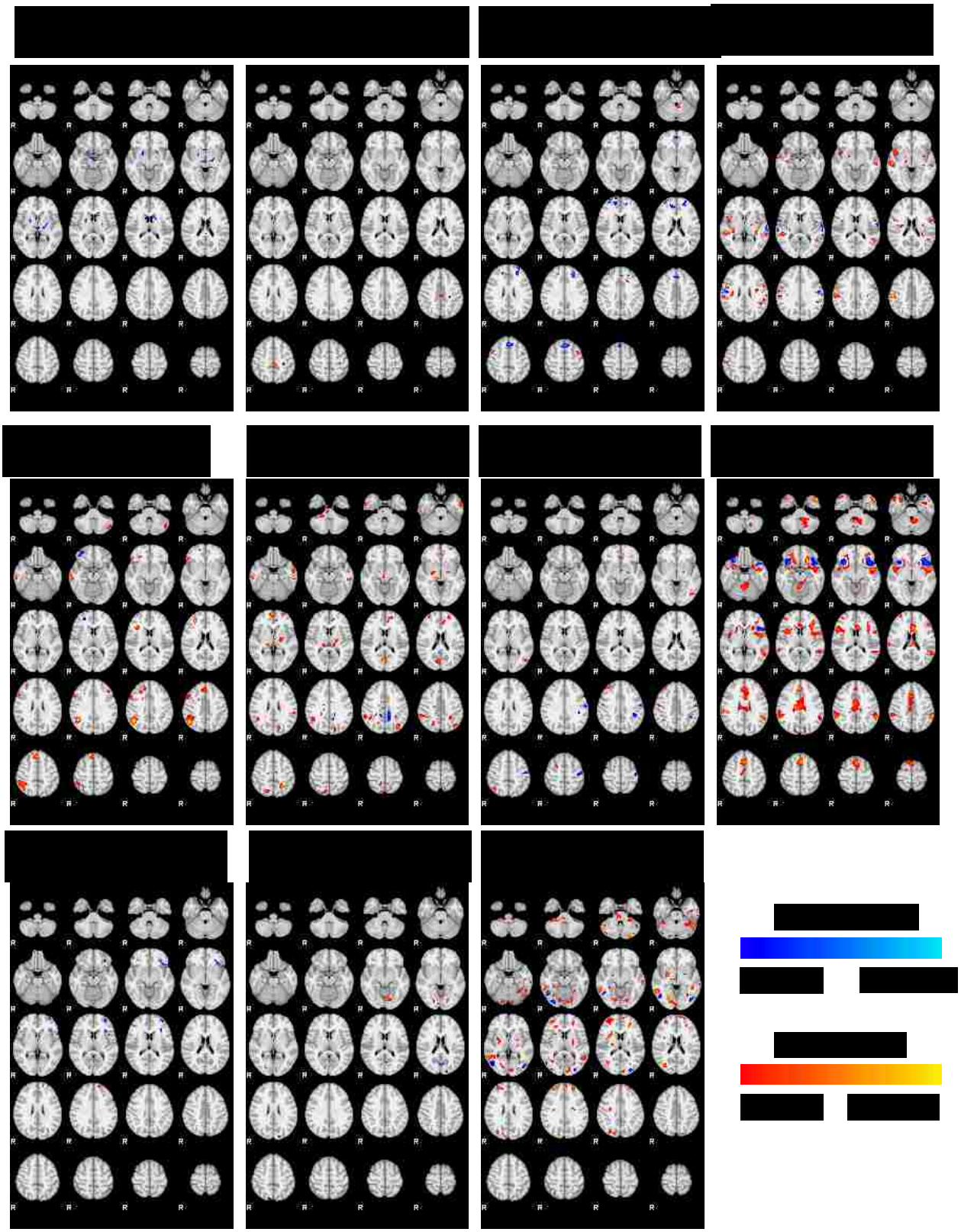
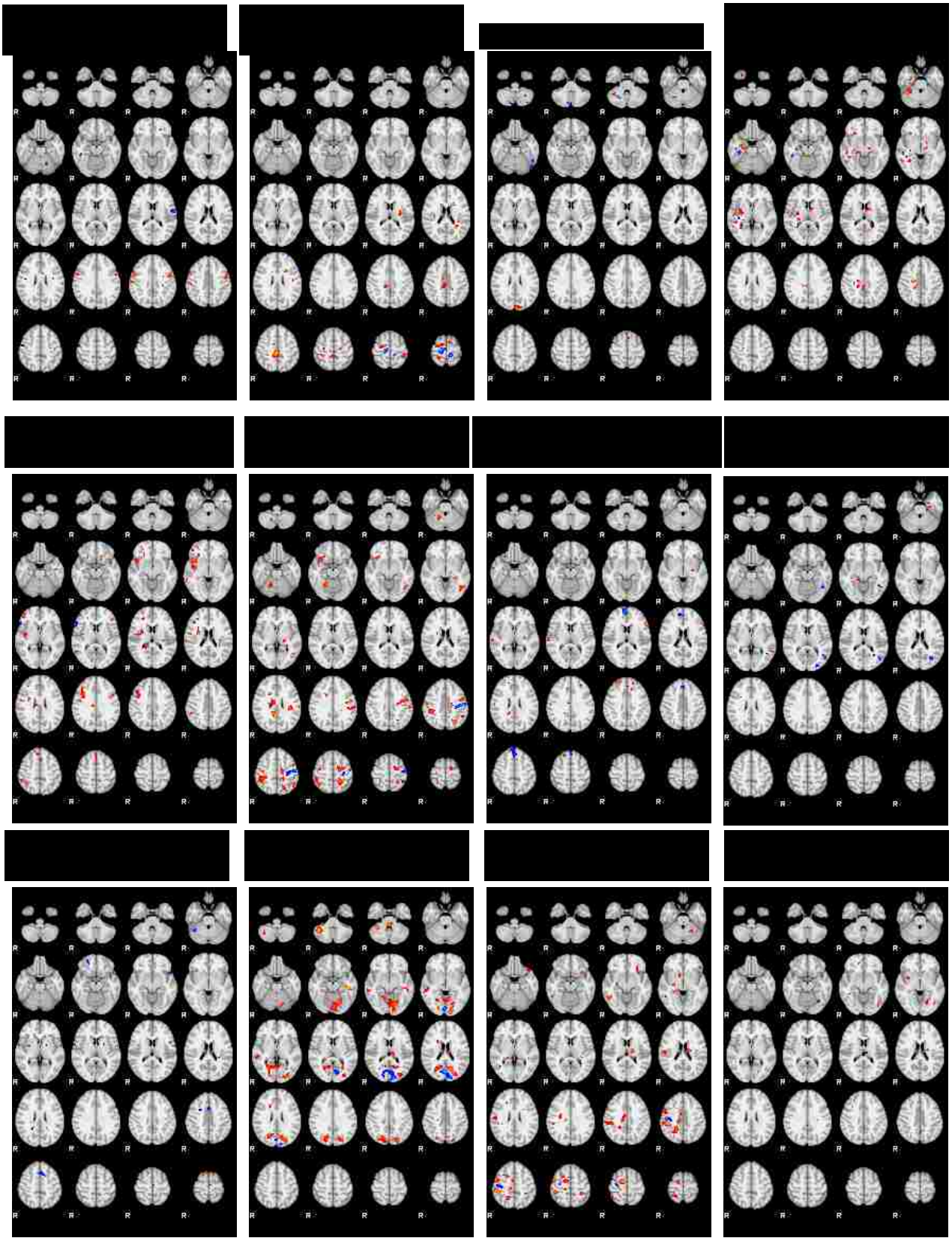


Figure 4. High order effect size maps with AUD>SD and SD>AUD contrasts



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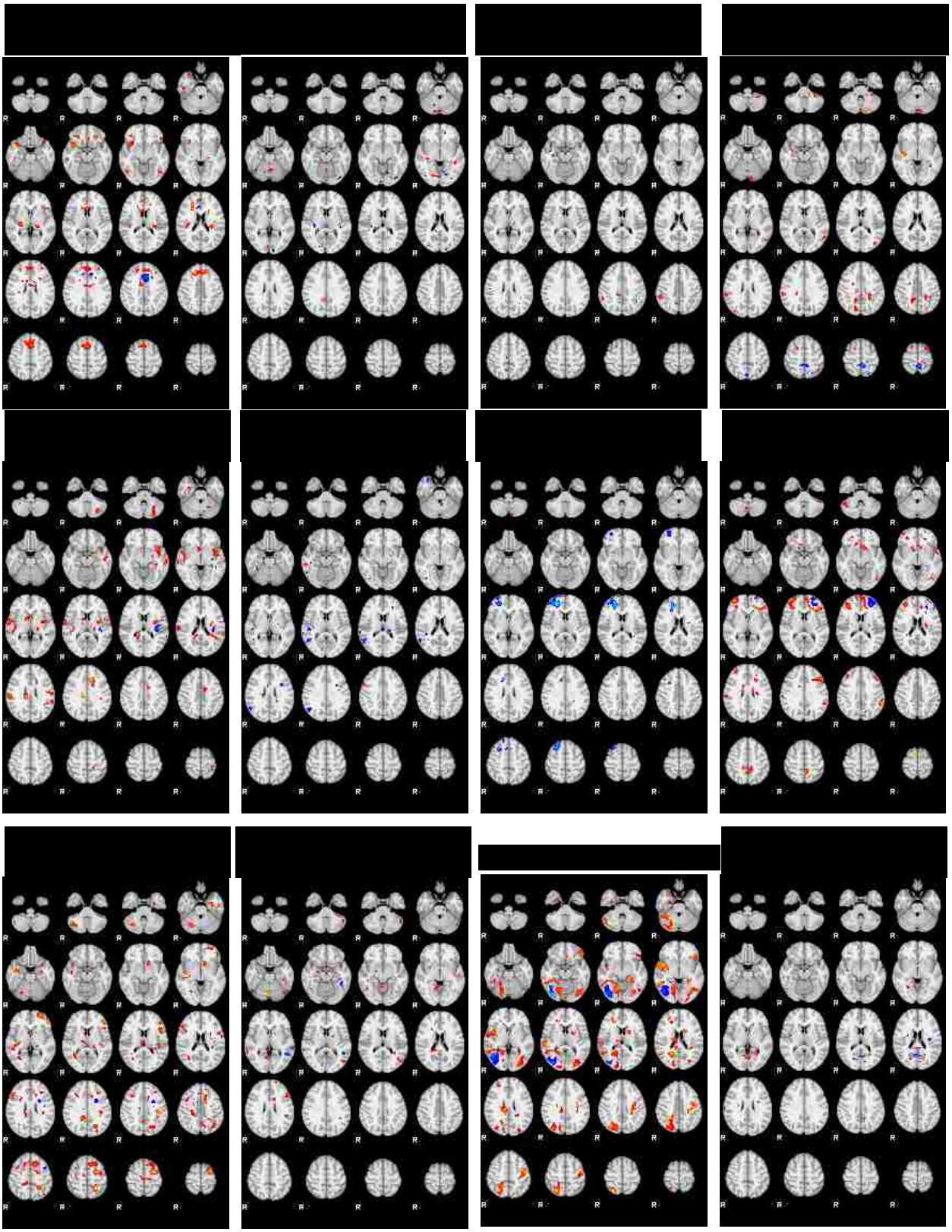

Figure 4. (continued)