Original Article

# Drinking severity mediates the relationship between hypothalamic connectivity and rule-breaking/intrusive behavior differently in young women and men: an exploratory study

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**Background:** The hypothalamus is a key hub of the neural circuits of motivated behavior. Alcohol misuse may lead to hypothalamic dysfunction. Here, we investigated how resting-state hypothalamic functional connectivities are altered in association with the severity of drinking and clinical comorbidities and how men and women differ in this association.

**Methods:** We employed the data of the Human Connectome Project. A total of 870 subjects were included in data analyses. The severity of alcohol use was quantified for individual subjects with the first principal component (PC1) identified from principal component analyses of all drinking measures. Rule-breaking and intrusive scores were evaluated with the Achenbach Adult Self-Report Scale. We performed a whole-brain regression of hypothalamic connectivities on drinking PC1 in all subjects and men/women separately and evaluated the results at a corrected threshold.

**Results:** Higher drinking PC1 was associated with greater hypothalamic connectivity with the paracentral lobule (PCL). Hypothalamic PCL connectivity was positively correlated with rule-breaking score in men ($r=0.152$, $P=0.002$) but not in women. In women but not men, hypothalamic connectivity with the left temporo-parietal junction (LTPJ) was negatively correlated with drinking PC1 ($r=-0.246$, $P<0.001$) and with intrusiveness score ($r=-0.127$, $P=0.006$). Mediation analyses showed that drinking PC1 mediated the relationship between hypothalamic PCL connectivity and rule-breaking score in men and between hypothalamic LTPJ connectivity and intrusiveness score bidirectionally in women.

**Conclusions:** We characterized sex-specific hypothalamic connectivities in link with the severity of alcohol misuse and its comorbidities. These findings extend the literature by elucidating the potential impact of problem drinking on the motivation circuits.

**Keywords:** Alcohol; rule-breaking; intrusive; resting state functional connectivity (rsFC); hypothalamus

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## Introduction

### *Hypothalamic functions and motivated behavior*

The hypothalamus regulates critical physiological functions, including sympathetic nervous activity and sleep-wake cycles, and supports a wide range of motivated behaviors (1). Orexin signaling in the hypothalamus transforms motivational states into behavior exploiting an opportunity or managing a threat (2). The hypothalamic neuropeptide oxytocin enhances social activities, including pair bonding and parental behaviors (3). Dysfunctional orexin or oxytocin signaling of the hypothalamus lead to antisocial behavior (4), rule-breaking and aggression (5), eating disorders (6), and addiction (2). Hypothalamic dysfunction may lead to motivational deficits, manifesting as psychomotor retardation, fatigue, weight/appetite changes, and a host of cognitive and affective problems, as observed in patients with depression (7). The hypothalamus shows strong connectivities with the amygdala, ventral medial prefrontal cortex, and ventral striatum, the "ventral" circuit that defines behavioral goals (8). Other studies show that, supported by dopaminergic signaling, hypothalamic projections to the ventral tegmental area are critical to motivated behavior (9). Together, there is abundant evidence that, via a myriad of neurochemical and circuit mechanisms, the hypothalamus maintains homeostasis and supports motivated behaviors (10).

### *Alcohol misuse and hypothalamic dysfunction*

Alcohol misuse disrupts the hypothalamus-pituitary-adrenal (HPA) axis and may result in stress intolerance, reproductive dysfunction, and behavioral disorders (11,12), including suicide (13). For instance, chronic drinking leads to hyperexcitability of glutamatergic corticotropin releasing hormone (CRH) neurons of the paraventricular nucleus in association with altered stress response during acute withdrawal (14). Notably, the hypothalamus also plays a critical role in regulating alcohol intake, likely through the interaction of orexigenic and anorexigenic neuropeptides (15). It is possible that hypothalamic dysfunction as a result of alcohol exposure would further compromise these regulatory circuits and aggravate problem drinking.

Chronic alcohol exposure compromises many component processes of motivated behaviors, including attentional and inhibitory control (16,17), win and loss processing (18,19), updating of action values (20), and self-efficacy in managing stress (21). Disrupted hypothalamic circuit function may contribute to comorbid clinical features of problem drinking. For instance, chronic drinking can lead to behavioral, social, and emotional apathy, a dysmotivational syndrome (22). As motivation is critical to the efficacy of cognitive behavioral therapy for drinkers, the effects of drinking on motivation could diminish the efficacy of behavioral treatments in individuals with alcohol use disorders (AUDs) (23). Further, In the spectrum of externalizing motivational traits, rule breaking and intrusive behavior has been associated with alcohol misuse (19,24). Another study documented the effects of parental problem drinking on adolescent alcohol use, aggression, and rule breaking over time (25). Investigating hypothalamic dysfunction would help in unraveling the pathophysiology of alcohol misuse and its comorbidities.

### *Resting state functional connectivity (rsFC)*

During resting the brain remains functionally and metabolically active. One manifestation of this activity concerns spontaneous fluctuations in the blood oxygenation level-dependent (BOLD) signals in functional magnetic resonance imaging (fMRI). The identification of correlation patterns in the spontaneous fluctuations or rsFC has transformed our understanding of brain organization and facilitated research of the neural markers of mental illnesses (26). Mapping of the rsFCs shows that the brain is organized into distinct functional networks, characterized by temporal dependency of the BOLD signals (27). The inter-regional connectivity has been used to refine functional subdivisions of brain areas (28) and identify neural markers of individual variation in clinical characteristics (29-33). Specifically, previous studies have characterized whole-brain hypothalamic rsFCs both in health and illness (34-37).

Studies have investigated the effects of acute and

 

chronic alcohol consumption on rsFC of the brain, both in humans (38) and in animals (39). Of direct relevance to the current study, altered hypothalamic connectivities were reported in association with social isolation and problem drinking (40). However, how alcohol misuse influences whole-brain hypothalamic connectivities and how altered hypothalamic connectivities may relate to ill-adaptive motivated behaviors comorbid with alcohol misuse have not been investigated.

### *Sex differences in externalizing traits and hypothalamic functional connectivity*

Research generally found higher levels of externalizing, including rule-breaking, behaviors in males than females (41). Our recent study also showed higher externalizing trait score in men than in women, and men revealed stronger relationship of externalizing trait and ventral striatal activation during monetary loss than women (42). Genetics may have contributed to the sex differences (43). Interestingly, males relative to females also appeared to be more vulnerable to the exposure to environmental toxins, including phthalate (44), bisphenol A (45), and heavy metals (46), in the development of rule-breaking behavior. Consistent with alcohol as a toxin, our previous work found that men young adult showed higher rule-breaking score than women, and the sex difference was significantly stronger in bingers compared with non-bingers (19).

Some studies documented sex differences in hypothalamic activities and connectivities. Men *vs.* women showed stronger structural connectivity of subgenual anterior cingulate cortex with the hypothalamus (47). Our recent study reported higher hypothalamus-insula rsFC in association with sleep deficiency as well as higher anxiety and depression scores in men but not in women (48). On the other hand, women may be more vulnerable to aberrant HPA axis responses to stress (49). For instance, in pathological gamblers watching a video of their preferred mode of gambling *vs.* a neutral video, women showed greater cortisol responses than men, although men had greater salivary cortisol concentrations at the baseline (50). Thus, while these previous findings do not allow us to formulate sex-specific hypotheses, it would be important to consider sex differences in investigating the hypothalamic rsFC correlates of alcohol misuse.

### *The present study*

We curated the Human Connectome Project (HCP) data and employed whole-brain regression of hypothalamic rsFC on "drinking PC1"—an index of alcohol use severity identified from principal component analysis of all drinking measures—in a cohort of over 800 participants. We identified the hypothalamic rsFC correlates and tested the inter-relationship between the rsFC and cognitive/emotional features available in the HCP. Finally, we performed mediation analyses to characterize the inter-relationship between PC1, hypothalamic rsFC, and those cognitive and emotional measures that were correlated with the rsFC. Because men and women are known to show differences in drinking severity and related psychopathologies (51-53), we conducted the same analyses for men and women separately as well. For rsFC identified from the whole sample or from men or women alone, we confirmed sex differences with slope tests. We discussed hypothalamic rsFC in link with alcohol misuse and clinical comorbidities as well as sex differences in the connectivity correlates.

## Methods

### *Dataset and demographics*

We employed the HCP 1,200 Subjects Release (S1200) data, collected from 2012 to 2015, in the current study. A total of 1096 young adults completed a resting state fMRI scan and, after exclusion of subjects missing physiological data (n=80) or not meeting the scrubbing criteria (n=146; details in "*Imaging protocol and preprocessing*"), 870 were retained. All subjects were physically healthy with no severe neurodevelopmental, neuropsychiatric or neurological disorders. Individuals may use alcohol to varying extents, which is known to influence brain structure and function (18,19,40,54-57). HCP evaluated alcohol use with multiple questions and, as in our earlier work, we conducted a principal component analysis of all drinking-related measures and identified a single, principal component (PC1) with an eigenvalue (7.44) >1 and explaining 49.58% of the variance. Age and sex were included as covariates in the analyses of all subjects and age was included as a covariate in the analyses of men and women separately. Data acquisition and sharing have been approved by the HCP parent IRB. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

### *Clinical and cognitive measures*

The HCP data comprised 15 inter-related drinking metrics

 

**Table 1** Demographics and clinical measures of the participants

| Characteristic | Men (n=406) | Women (n=464) | *t* | P value* |
|---|---|---|---|---|
| Age (years) | 27.7±3.6 | 29.4±3.6 | −6.88 | <0.001 |
| Race (White/AA/AH/AI/more/unknown) | 313/48/28/1/12/4 | 346/66/32/0/11/9 | – | – |
| Ethnicity (Latino/non-Latino/unknown) | 42/359/5 | 32/427/5 | – | – |
| Drinking PC1 | 0.37±1.08 | −0.32±0.79 | 9.75 | <0.001^ |
| Rule-breaking score | 3.3±3.2 | 1.8±2.2 | 6.90 | <0.001^ |
| Intrusive score | 2.6±2.3 | 2.1±2.0 | 3.19 | 0.001^ |

Data are represented as mean ± standard deviation or number of subjects. *, two-sample *t*-test (^ with age as a covariate). AA, African American or Black; AH, Asian or Native Hawaiian; AI, Native Alaskan or Indian American; more, more than one race; unknown, unknown or not reported; Latino, Hispanic/Latino; non-Latino, not Hispanic/Latino; drinking PC1, the first principal component obtained of principal component analyses of all drinking measures.

to assess the severity of alcohol use. Table S1 shows the mean ± standard deviation (SD) of the drinking measures and PC1 identified of principal component analysis of these measures. All participants were assessed with the Achenbach Adult Self Report (ASR) syndrome scales. Briefly, the ASR is a 126-item self-report questionnaire for adults (ages 18 to 59 years) assessing aspects of adaptive functioning and problems. The questionnaire provides scores for the following syndrome scales: anxious/depressed, withdrawn, somatic complaints, thought problems, attention problems, aggressive behavior, rule-breaking behavior, and intrusive behavior. With respect to the current findings (please see Results), the rule-breaking subscale (Appendix 1) comprises 14 items, each scored from 0 to 2, so the score sums from 0 to 28, with a higher score indicating more severe rule-breaking behavior. The intrusive subscale (Appendix 1) comprises 6 items, each scored from 0 to 2, so the score sums from 0 to 12, with a higher score indicating more severe intrusive problem.

*Table 1* shows age, race and ethnicity, drinking PC1, rule-breaking and intrusive scores of men and women separately.

### *Imaging protocol and preprocessing*

MRI was done using a customized 3 T Siemens Connectome Skyra with a standard 32-channel Siemens receiver head coil and a body transmission coil. T1-weighted high-resolution structural images were acquired using a three-dimensional (3D) magnetization prepared rapid acquisition gradient (MPRAGE) sequence with 0.7 mm isotropic resolution [field of view (FOV) =224×224 mm, matrix =320×320, 256 sagittal slices, repetition time (TR) =2,400 ms, echo time (TE) =2.14 ms, inversion time (TI) =1,000 ms, flip angle (FA) =8°]. FMRI data were collected using gradient-echo echo-planar imaging (EPI) with 2.0 mm isotropic resolution (FOV =208×180 mm, matrix =104×90, 72 slices, TR =720 ms, TE =33.1 ms, FA =52°, multi-band factor =8). Preprocessing steps are same with our recent work (48,58).

### *rsFC of the hypothalamus*

The mask of the hypothalamus (*Figure 1*) was obtained from the WFU Pick Atlas (http://fmri.wfubmc.edu/software/pickatlas) (59) and used as the seed region. Whole-brain voxel-wise analyses were conducted to compute the rsFC of hypothalamus. The BOLD time courses of each voxel were averaged, and the correlation coefficient was computed between the average time course of all voxels of the seed and the time courses of all other voxels of the brain for individual participants.

In group analyses, a whole-brain regression of seed-based hypothalamus rsFC against PC1 was conducted in men and women combined, with age and sex as covariates, as well as separately, with age as a covariate. The results were evaluated at voxel P<0.001, uncorrected, in combination with a cluster P<0.05, corrected for family-wise error (FWE) of multiple comparisons, on the basis of Gaussian random field theory, as implemented in SPM, following the reporting standards (60).

For the regions of interest (ROIs) identified from linear regressions, we used MarsBar (http://marsbar.sourceforge.net/) to derive for individual subjects the β estimates of the rsFCs. We then tested sex differences in the regressions

 

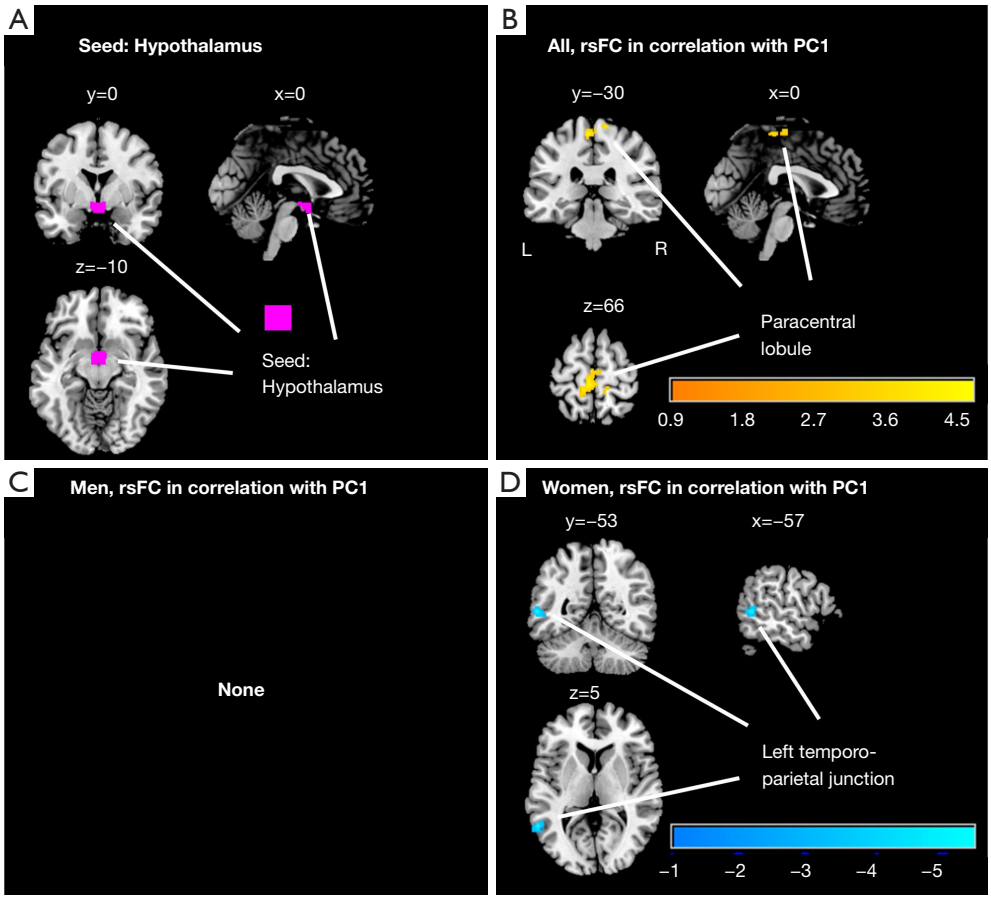


**Figure 1** Brian regions showing hypothalamus connectivity in correlation with PC1. (A) Seed: hypothalamus; (B) in all subjects, a cluster in the paracentral lobule showing hypothalamic rsFC in positive correlation with the PC1; (C) in men, no cluster survived at the same threshold; (D) in women, a cluster in the left temporo-parietal junction showing hypothalamic rsFC in negative correlation with the PC1. Color bar, voxel T value. rsFC, resting state functional connectivity; PC1, the first principal component obtained of principal component analyses of all drinking measures; L, left; R, right.

using slope tests, with age as a covariate (61). Note that the slope tests of sex differences were not "double-dipping" (62,63), as the regression maps were identified with a threshold and a cluster showing correlation in men could also show a correlation in women that just missed the threshold to be identified from whole-brain regression, and vice versa. Thus, direct tests of the slopes were needed to confirm sex differences.

### *Mediation analyses*

We performed mediation analyses following published routines (64,65), as detailed earlier (66,67), to evaluate the relationships between neural markers, rule-breaking score, and PC1 in men, and the relationships between neural markers, intrusiveness score, and PC1 in women (see Results). Briefly, in a mediation analysis, the relation between the independent variable X and dependent variable Y; that is, X → Y is tested to determine whether it is significantly mediated by a variable M. The results of mediation analyses did not imply causality. Rather, the findings served to clarify the inter-relationships of multiple, correlating variables.

## Results

### *Neural correlates of PC1: hypothalamus rsFC*

At voxel P<0.001, uncorrected in combination with cluster P<0.05, FWE-corrected, a whole-brain linear regression

 

of the hypothalamus rsFCs against PC1 across all subjects showed a cluster in the paracentral lobule (PCL, x, y, z =–4, –32, 66; Z=4.49, 2,440 $mm^3$; *Figure 1B*) showed a significant positive correlation with the PC1. The same analyses for men did not reveal significant findings in men alone (*Figure 1C*). In women alone, a cluster in the left temporo-parietal junction (LTPJ, x, y, z =–58, –54, 4; Z=5.33, 824 $mm^3$; *Figure 1D*) showed a significant negative correlation with the PC1.

### *Clinical measures*

PC1 showed significant difference between men and women (t=9.75, P<0.001). Rule-breaking and intrusive score was higher in men than women (t=6.90, P<0.001; t=3.19, P=0.001, respectively). Table S2 shows the results of sex differences on other Achenbach ASR measures.

PC1 showed a significant correlation with rule-breaking score (all: r=0.33, P<0.001; men: r=0.37, P<0.001; women: r=0.26, P<0.001) with age as a covariate; in a slope test men and women did not differ in the slope of regression (Z=1.79, P=0.074; *Figure 2A*). PC1 score also showed a significant correlation with intrusive score (all: r=0.18, P<0.001; men: r=0.16, P=0.001; women: r=0.21, P<0.001) with the same covariate; likewise, men and women did not differ in the slope of regression in a slope test (Z=–0.76, P=0.447; *Figure 2A*). Table S3 shows the results of correlation of PC1 and other clinical measures.

### *Correlation of rsFC and clinical measures*

The $\beta$ estimate of the hypothalamus-PCL rsFC was significantly correlated with PC1 in all (r=0.167, P<0.001), men (r=0.174, P<0.001), and women (r=0.170, P<0.001) subjects in a linear regression with age as a covariate. In a slope test men and women did not differ in the slope of regression (Z=0.06, P=0.952; *Figure 2B*, left panel). The $\beta$ estimate of the hypothalamus-LTPJ rsFC was significantly correlated with PC1 in all (r=–0.125, P<0.001) and women (r=–0.246, P<0.001), but not in men (r=–0.036, P=0.466) in a linear regression with age as a covariate. In a slope test men and women differed significantly in the slope of regression (Z=3.15, P=0.0016; *Figure 2B*, right panel).

The $\beta$ estimates of hypothalamus-PCL rsFC were significantly correlated with rule-breaking score in all (r=0.088, P=0.009) and men (r=0.152, P=0.002), but not in women (r=–0.006, P=0.898) in a linear regression with age as a covariate. In slope tests men and women differed significantly in the slope of regression (Z=2.33, P=0.0198; *Figure 2C*, left panel). The $\beta$ estimates of hypothalamus-PCL rsFC were not correlated with intrusive score in all, men, or women (all P values >0.119). Table S4 shows the results of correlation of hypothalamus-PCL rsFC and other clinical measures.

The $\beta$ estimates of hypothalamus-LTPJ rsFC were not correlated with rule-breaking score in all, men, or women (all P's >0.259). The $\beta$ estimates of hypothalamus-LTPJ rsFC were significantly correlated with intrusive score in women (r=–0.127, P=0.006), but not in all (r=–0.065, P=0.055) or men (r=–0.013, P=0.794) in a linear regression with age as a covariate. In slope tests men and women did not differ in the slope of regression (Z=1.68, P=0.093; *Figure 2C*, right panel). Table S5 shows the results of correlation of hypothalamus-LTPJ rsFC and other clinical measures.

### *Inter-relationship of hypothalamus-PCL and LTPJ rsFC, drinking PC1, and rule-breaking/intrusive scores*

In men, individual drinking PC1, rule-breaking score, and rsFC of hypothalamus-PCL (HT-PCL $\beta$) were positively correlated pairwise. We performed a mediation analysis to examine the inter-relationship between the PC1, rule-breaking score, and HT-PCL $\beta$, with age as a covariate. We considered all six models and employed a corrected P (0.05/6=0.0083) to evaluate the mediation effects. One model (HT-PCL $\beta$ → PC1 → rule-breaking score) showed significant and complete mediation, on the contrast, we also plot the model (rule-breaking score → PC1 → HT-PCL $\beta$; *Figure 3A*; statistics in *Table 2*).

Likewise, we performed a mediation analysis to examine the inter-relationship between the PC1 score, intrusive score, and HT-LTPJ $\beta$, with age as a covariate in women. Two models (intrusive score → PC1 score → HT-left TPJ $\beta$; HT-LTPJ $\beta$ → PC1 score → intrusive score) showed significant and complete mediation (*Figure 3B*; statistics in *Table 3*).

## Discussion

Higher drinking PC1 was associated with greater hypothalamic connectivity with the PCL. Hypothalamic PCL connectivity was also positively correlated with rule-breaking score in men but not in women, with the sex difference confirmed by a slope test. In women but not men, hypothalamic connectivity with the LTPJ was negatively

 

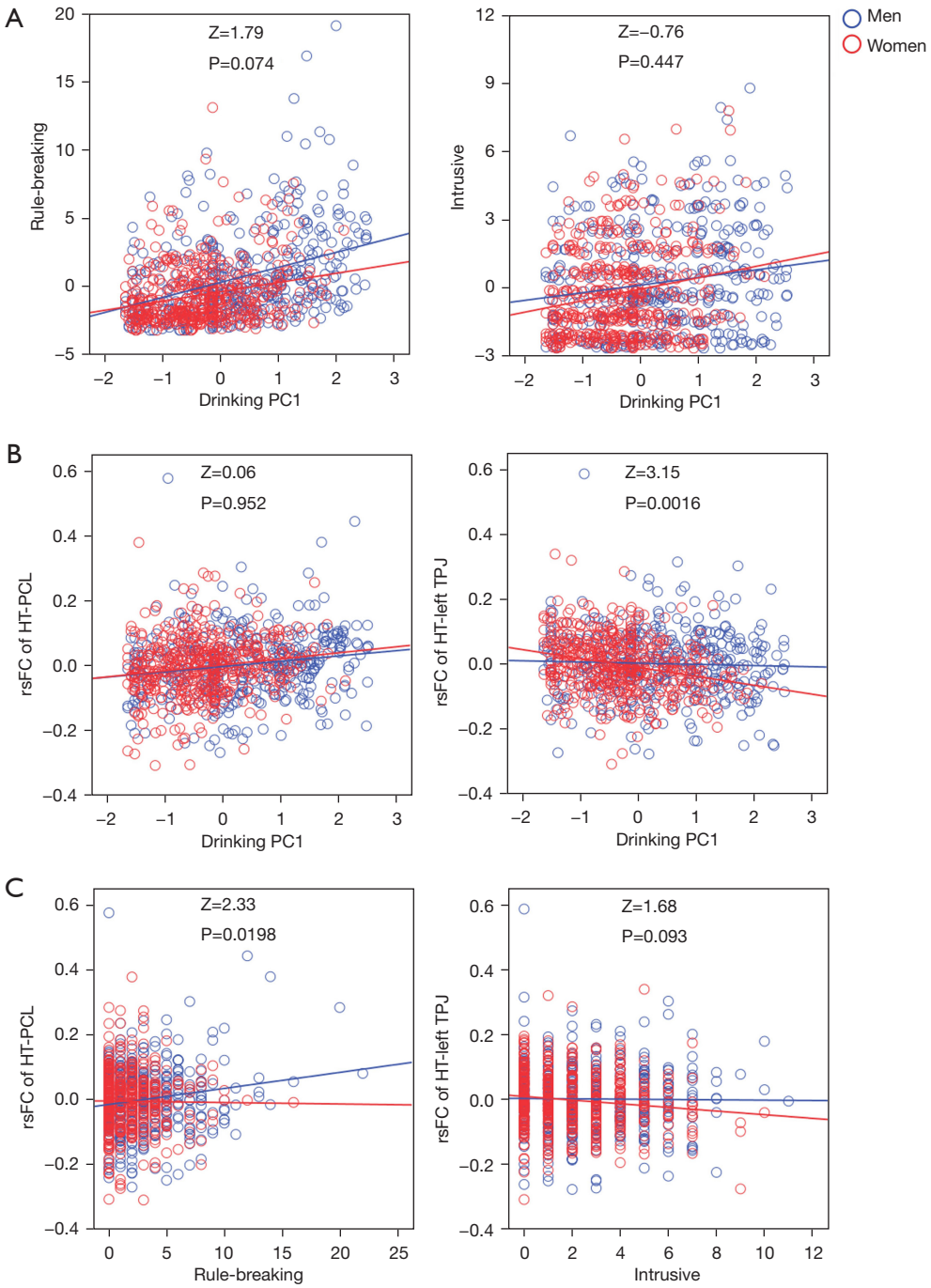


**Figure 2** Scatter plot of rsFC and clinical measures. (A) Linear regression of rule-breaking and of intrusive *vs.* PC1 in men (blue) and women (red) subjects; (B) linear regression of hypothalamus-PCL and -left TPJ rsFC *vs.* PC1; (C) hypothalamus-PCL rsFC *vs.* rule-breaking, and hypothalamus-left TPJ rsFC *vs.* intrusive score. Z and P values reflect the tests of slope differences in the regression. Note that the residuals are plotted here with age accounted for in all regressions. Drinking PC1, the first principal component obtained of principal component analyses of all drinking measures; rsFC, resting state functional connectivity; HT, hypothalamus; PCL, paracentral lobule; TPJ, temporo-parietal junction.

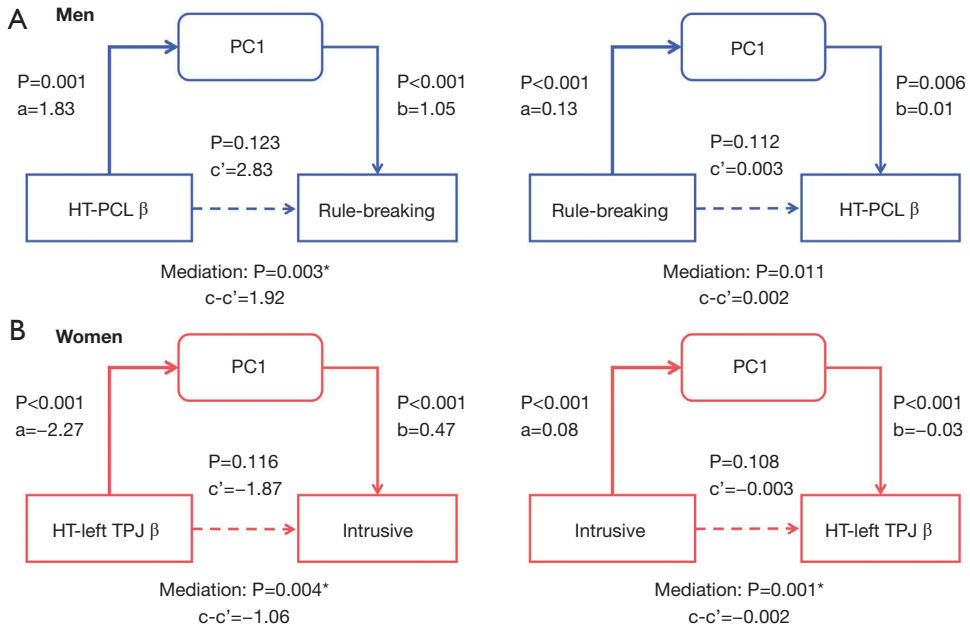


**Figure 3** Mediation analyses: PC1 completely mediated the correlation (A) between HT-PCL $\beta$ and rule-breaking score in men; and (B) between HT-left TPJ $\beta$ and intrusive score in women. Mediation *, P<0.05/6=0.0083. PC1, the first principal component obtained of principal component analyses of all drinking measures; HT, hypothalamus; PCL, paracentral lobule; TPJ, temporo-parietal junction.

**Table 2** Mediation statistics of PC1, rule-breaking and HT-PCL $\beta$ in men

| Models | Path a (X→M) | Path b (M→Y) | Path c (X→Y) | Path c' (X→Y) | Mediation Path (c-c') |
|---|---|---|---|---|---|
| Model 1: X (rsFC-PCL)→Y (PC1) mediated by M (ASR_Rule) | | | | | |
| $\beta$ | 4.753 | 0.119 | 1.826 | 1.262 | 0.564 |
| P | 0.021 | 0.000 | 0.001 | 0.014 | 0.018 |
| Model 2: X (rsFC-PCL)→Y (ASR_Rule) mediated by M (PC1)* | | | | | |
| $\beta$ | 1.826 | 1.052 | 4.753 | 2.832 | 1.921 |
| P | 0.001 | 0.000 | 0.021 | 0.123 | 0.003* |
| Model 3: X (PC1)→Y (rsFC-PCL) mediated by M (ASR_Rule) | | | | | |
| $\beta$ | 1.099 | 0.003 | 0.017 | 0.013 | 0.004 |
| P | 0.000 | 0.112 | 0.000 | 0.006 | 0.132 |
| Model 4: X (PC1)→Y(ASR_Rule) mediated by M (rsFC-PCL) | | | | | |
| $\beta$ | 0.017 | 2.832 | 1.099 | 1.052 | 0.047 |
| P | 0.000 | 0.123 | 0.000 | 0.000 | 0.214 |
| Model 5: X (ASR_Rule)→Y(PC1) mediated by M (rsFC-PCL) | | | | | |
| $\beta$ | 0.005 | 1.262 | 0.125 | 0.119 | 0.006 |
| P | 0.014 | 0.014 | 0.000 | 0.000 | 0.090 |
| Model 6: X (ASR_Rule)→Y(rsFC-PCL) mediated by M (PC1) | | | | | |
| $\beta$ | 0.125 | 0.013 | 0.005 | 0.003 | 0.002 |
| P | 0.000 | 0.006 | 0.014 | 0.112 | 0.011 |

Model 2 showed significant mediation * (P for path c-c' <0.05/6=0.0083). PC1, the first principal component obtained of principal component analyses of all drinking measures; HT, hypothalamus; PCL, paracentral lobule; rsFC, resting state functional connectivity; ASR, Achenbach Adult Self-Report.

**Table 3** Mediation statistics of PC1, intrusive and HT-left TPJ $\beta$ in women

| Models | Path a (X→M) | Path b (M→Y) | Path c (X→Y) | Path c' (X→Y) | Mediation Path (c-c') |
|---|---|---|---|---|---|
| Model 1: X (rsFC-left TPJ)→Y (PC1) mediated by M (ASR_Intr) | | | | | |
| $\beta$ | –2.935 | 0.069 | –2.265 | –2.061 | –0.204 |
| P | 0.013 | 0.000 | 0.000 | 0.000 | 0.045 |
| Model 2: X (rsFC-left TPJ)→Y (ASR_Intr) mediated by M (PC1)* | | | | | |
| $\beta$ | –2.265 | 0.468 | –2.935 | –1.874 | –1.061 |
| P | 0.000 | 0.000 | 0.013 | 0.116 | 0.004* |
| Model 3: X (PC1)→Y (rsFC-left TPJ) mediated by M (ASR_Intr) | | | | | |
| $\beta$ | 0.520 | –0.003 | –0.027 | –0.026 | –0.002 |
| P | 0.000 | 0.108 | 0.000 | 0.000 | 0.140 |
| Model 4: X (PC1)→Y(ASR_Intr) mediated by M (rsFC-left TPJ) | | | | | |
| $\beta$ | –0.027 | –1.874 | 0.520 | 0.468 | 0.051 |
| P | 0.000 | 0.116 | 0.000 | 0.000 | 0.128 |
| Model 5: X (ASR_Intr)→Y(PC1) mediated by M (rsFC-left TPJ) | | | | | |
| $\beta$ | –0.006 | –2.061 | 0.081 | 0.069 | 0.011 |
| P | 0.008 | 0.000 | 0.000 | 0.000 | 0.018 |
| Model 6: X (ASR_Intr)→Y(rsFC-left TPJ) mediated by M (PC1)* | | | | | |
| $\beta$ | 0.081 | –0.026 | –0.006 | –0.003 | –0.002 |
| P | 0.000 | 0.000 | 0.008 | 0.108 | 0.001* |

Model 2 and Model 6 showed significant mediation * (P for path c-c' <0.05/6=0.0083). PC1, the first principal component obtained of principal component analyses of all drinking measures; TPJ, temporo-parietal junction; HT, hypothalamus; rsFC, resting state functional connectivity; ASR, Achenbach Adult Self-Report.

correlated with drinking PC1 and with intrusiveness score, and slope tests confirmed sex difference in the former. Mediation analyses showed that drinking PC1 mediated the relationship between hypothalamic PCL connectivity and rule-breaking score in men and bidirectionally between hypothalamic LTPJ connectivity and intrusiveness score in women. We discussed the main findings in the below.

### *Hypothalamic connectivity with the PCL*

The hypothalamus does not appear to have direct anatomical connections with the PCL. On the other hand, likely through indirect connections, altered hypothalamic PCL connectivities or co-activations were reported across a number of physiological conditions, including sexual orgasm (68) and electrical stimulation of the auricular branch of the vagus nerve (69). These studies suggest broad physiological and potentially pathophysiological importance of the hypothalamic PCL circuits. In particular, in a study to investigate the directed interactions between resting-state brain activity and autonomic nervous system outflow with concurrent fMRI and physiological recordings, investigators demonstrated a role of the amygdala, hypothalamus, and PCL, amidst other structures, in autonomic regulation (70). The latter findings highlight the potential contribution of the hypothalamic PCL connectivity to autonomic signaling, which along with neuroendocrine stress response, is known to be disrupted in problem drinkers (71).

The PCL comprises most of the somatomotor cortex and supports somatosensation and interoception. Individuals with AUDs are known to demonstrate a myriad of somatosensory and motor symptoms and signs (72). Animal studies likewise provide ample evidence for altered somatomotor functions as a consequence of chronic alcohol exposure (73,74). Further, the somatomotor circuit is implicated in cue-elicited alcohol craving, conflict control, as

 

well as alcohol expectancy (75-78), psychological processes central to alcohol misuse. Here, we observed that the severity of drinking, as reflected in PC1, was significantly correlated with both rule-breaking and intrusiveness scores and that hypothalamic PCL connectivity was associated with rule-breaking in men. In support, the somatomotor network has been widely implicated in impulsive behaviors (79-82). Thus, during motivated behavior, which is typically highly arousing, hypothalamic PCL connectivity may elevate in the manifestation of individual traits of rule-breaking.

### *Hypothalamic connectivity with the TPJ*

The hypothalamus showed lower functional connectivity with the LTPJ in women with more severe drinking and intrusive behavior, a sign of dysfunctional social interaction. The hypothalamus does not have direct anatomical connections with the TPJ, either. However, hypothalamic-temporal-parietal cortical activity and/or connectivity has been associated with major depression (83), eating disorders (84), exposure to high *vs.* low calorie food cues (85) or to video sexual stimulation (86) or evaluation of bodily expressions during social interactions (87), and adaptive responses to social touch in link with plasma levels of oxytocin, a hormone secreted by the hypothalamus (88). In an animal study, local cerebral glucose utilization rates were higher in the hypothalamus, ventral tegmental area, nucleus accumbens, and temporal parietal cortices in alcohol-preferring relative to non-preferring rats (89). Notably, both the hypothalamus and temporo-parietal cortex exhibited sexual dimorphism in gray matter volumes, possibly as a result of modulation by testosterone (90). Although the implication remains unclear, the latter finding can be considered along with the observation here of a significant correlation of hypothalamic TPJ connectivity with drinking PC1 in women but not in men.

### *Sex differences in hypothalamic connectivity and alcohol use*

We explored sex differences in how hypothalamic connectivities were altered in relation to the severity of alcohol misuse by examining the data of men and women separately. Men but not women showed higher hypothalamic PCL connectivity and women but not men showed lower hypothalamic LTPJ connectivity in association with more severe drinking, with the latter sex difference confirmed by slope tests. The sex difference also extended to the relationship between hypothalamic connectivities and rule-breaking behavior, as discussed briefly earlier. We wish to note that rule-breaking and social intrusiveness may both reflect disrupted social behaviors comorbid with alcohol misuse although they appear to manifest differently across sexes and involve distinct hypothalamic connectivity correlates, as the current findings suggest. These findings suggest potentially sex-specific pathways whereby the hypothalamic circuits are involved in problem drinking and its behavioral comorbidities. The sex-different findings also suggest the importance of comprehensive screening of different dimensions (e.g., rule-breaking *vs.* social intrusion) a behavioral construct (e.g., impulsivity) to unravel their potential clinical implications.

### *Limitations of the study*

Several limitations need to be considered for the current study. First, the findings of mediation analyses only suggest directional influences. Longitudinal studies will provide evidence testing the link between hypothalamic connectivity, drinking, and its behavioral comorbidity. Second, although alcohol use severity varied significantly across individuals, the HCP data represent largely a non-clinical sample. Thus, whether the current findings extend to individuals with moderate and severe AUDs remains to be investigated. Third, rsFC represents one neural marker of alcohol misuse. In view of the current findings, task-related regional activities and connectivities during social interaction may provide additional information of the hypothalamus-related neural processes compromised by problem drinking.

## Conclusions

In conclusion, the current study extends the literature by highlighting the roles of hypothalamic circuit dysfunction in alcohol misuse, impulsivity, and deficits in social cognition. The sex-specific connectivity correlates warrant more investigation to further our knowledge of the heterogeneity in the pathophysiological processes of alcohol misuse and its many behavioral comorbidities.

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## Footnote

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-24-815/coif). J.B. and C.S.R.L. received NIH grant (No. DA051922). The other authors have no conflicts of interest to declare.

*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Data acquisition and sharing have been approved by the HCP parent IRB. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).



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Supplementary

## Appendix 1

*Items of Achenbach Adult Self-Report (ASR)*

Participants were required to circle 0 (not true), 1 (somewhat or sometimes true), or 2 (very or often true) for each item to describe themselves over the past 6 months.

*Rule-breaking behavior subscale*

1. I use drugs (other than alcohol and nicotine) for non-medical purposes.
2. I damage or destroy my things.
3. I break rules at work or elsewhere.
4. I don't feel guilty after doing something I shouldn't.
5. I hang around people who get in trouble.
6. I am impulsive or act without thinking.
7. I lie or cheat.
8. My behavior is irresponsible.
9. I steal.
10. I drink too much alcohol or get drunk.
11. I do things that may cause me trouble with the law.
12. I fail to pay my debts or meet other financial responsibilities.
13. I have trouble managing money or credit cards.
14. I have trouble keeping a job.

*Intrusive subscale*

1. I brag.
2. I try to get a lot of attention.
3. I show off or clown.
4. I talk too much.
5. I tease others a lot.
6. I am louder than others.


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**Table S1** Drinking variables of men and women

| Characteristic | Men (n=406) | Women (n=464) | *t* | P value* |
|---|---|---|---|---|
| SSAGA_Alc_D4_Dp_Sx | 0.77±0.98 | 0.37±0.64 | 6.64 | 0.000 |
| SSAGA_Alc_D4_Ab_Dx | 1.79±1.59 | 1.41±1.22 | 3.83 | 0.000 |
| SSAGA_Alc_D4_Ab_Sx | 0.38±0.67 | 0.16±0.45 | 5.46 | 0.000 |
| SSAGA_Alc_D4_Dp_Dx | 1.37±1.15 | 1.12±0.69 | 3.68 | 0.000 |
| SSAGA_Alc_12_Drinks_Per_Day | 2.78±1.71 | 1.72±1.2 | 9.07 | 0.000 |
| SSAGA_Alc_12_Frq | −3.9±1.67 | −4.55±1.39 | 5.79 | 0.000 |
| SSAGA_Alc_12_Frq_5plus | −3.4±1.28 | −4.12±0.98 | 7.98 | 0.000 |
| SSAGA_Alc_12_Frq_Drk | −2.83±0.99 | −3.29±0.71 | 6.62 | 0.000 |
| SSAGA_Alc_12_Max_Drk | 3.61±2.07 | 2.2±1.29 | 10.22 | 0.000 |
| SSAGA_Alc_Age_1st_Use | 3.05±1.29 | 3.12±1.32 | −0.95 | 0.342 |
| SSAGA_Alc_Hvy_Drinks_Per_Day | 3.88±1.73 | 2.81±1.58 | 8.72 | 0.000 |
| SSAGA_Alc_Hvy_Frq | −3.08±1.81 | −3.69±1.67 | 5.19 | 0.000 |
| SSAGA_Alc_Hvy_Frq_5plus | −2.62±1.41 | −3.34±1.37 | 7.12 | 0.000 |
| SSAGA_Alc_Hvy_Frq_Drk | −2.12±1.11 | −2.51±1.1 | 4.76 | 0.000 |
| SSAGA_Alc_Hvy_Max_Drinks | 4.32±2.03 | 2.6±1.42 | 12.98 | 0.000 |
| PC1 | 0.37±1.08 | −0.32±0.79 | 9.75 | 0.000 |

Data are represented as mean ± standard deviation. *, two-sample *t*-test (with age as a covariate). Because men and women differed significantly in age, age was included as a covariate in all analyses. SSAGA_Alc_D4_Dp_Sx (Number of DSM4 Alcohol Dependence Criteria Endorsed), SSAGA_Alc_D4_Ab_Dx (DSM4 Alcohol Abuse Criteria Met), SSAGA_Alc_D4_Ab_Sx (DSM4 Alcohol Abuse number of symptoms), SSAGA_Alc_D4_Dp_Dx (DSM4 Alcohol Dependence Criteria Met), SSAGA_Alc_12_Drinks_Per_Day (Drinks per drinking day in past 12 months), SSAGA_Alc_12_Frq (Frequency of any alcohol use in past 12 months), SSAGA_Alc_12_Frq_5plus (Frequency of drinking 5+ drinks in past 12 months), SSAGA_Alc_12_Frq_Drk (Frequency drunk in past 12 months), SSAGA_Alc_12_Max_Drk (Max drinks in a single day in past 12 months), SSAGA_Alc_Age_1st_Use (Age at first alcohol use: <15=1, 15-16=2, 17-18=3, 19-20=4, 21+=5), SSAGA_Alc_Hvy_Drinks_Per_Day (Drinks per day in heaviest 12-month period), SSAGA_Alc_Hvy_Frq (Frequency of any alcohol use, heaviest 12-month period), SSAGA_Alc_Hvy_Frq_5plus (Frequency of drinking 5+ drinks, heaviest 12-month period), SSAGA_Alc_Hvy_Frq_Drk (Frequency drunk in heaviest 12-month period), SSAGA_Alc_Hvy_Max_Drinks (Lifetime max drinks in single day), PC1 (Severity of alcohol use as quantified by the weight of the first principal component of PCA of all 15 drinking measures). Note that SSAGA_Alc_12_Frq, SSAGA_Alc_12_Frq_5plus, SSAGA_Alc_12_Frq_Drk, SSAGA_Alc_Hvy_Frq, SSAGA_Alc_Hvy_Frq_5plus and SSAGA_Alc_Hvy_Frq_Drk were flipped, so these entries are negative in value because the original scales needed to be reversed in scoring so that across metrics, a higher value reflects more severe alcohol misuse, to be consistent.


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**Table S2** ASR measures of men and women

| Characteristic | Men (n=406) | Women (n=464) | *t* | P value* |
|---|---|---|---|---|
| Anxious/Depressive | 5.74±5.40 | 6.05±5.27 | –1.27 | 0.206 |
| Withdrawn | 2.76±2.45 | 1.83±2.07 | 5.10 | 0.000 |
| Somatic complaints | 2.23±2.63 | 2.69±2.89 | –2.30 | 0.022 |
| Thought problems | 2.26±2.18 | 1.99±2.06 | 0.66 | 0.507 |
| Attention problems | 6.78±4.44 | 5.91±4.17 | 2.36 | 0.019 |
| Aggressive behavior | 3.98±3.42 | 3.45±3.12 | 1.95 | 0.051 |
| Rule breaking | 3.29±3.22 | 1.80±2.19 | 6.90 | 0.000 |
| Intrusive | 2.62±2.25 | 2.08±2.00 | 3.19 | 0.001 |
| Other problems | 9.75±4.82 | 8.60±4.25 | 2.63 | 0.009 |
| Critical items | 4.50±3.46 | 3.50±2.82 | 3.62 | 0.000 |
| Internalizing | 10.73±9.05 | 10.58±8.56 | –0.18 | 0.861 |
| Externalizing | 9.89±7.18 | 7.33±5.71 | 4.96 | 0.000 |

Data are represented as mean ± standard deviation. *, two-sample *t*-test (with age as a covariate). ASR, Achenbach Adult Self-Report.


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**Table S3** Correlation of PC1 and ASR measures

| Characteristic | Men (n=406) | Women (n=464) | All (n=870) |
|---|---|---|---|
| Anxious/depressive | | | |
| r | −0.01 | 0.09 | 0.04 |
| P | 0.916 | 0.065 | 0.286 |
| Withdrawn | | | |
| r | −0.04 | −0.03 | −0.03 |
| P | 0.453 | 0.547 | 0.353 |
| Somatic complaints | | | |
| r | 0.07 | 0.08 | 0.07 |
| P | 0.170 | 0.097 | 0.029 |
| Thought problems | | | |
| r | 0.07 | 0.03 | 0.06 |
| P | 0.188 | 0.492 | 0.094 |
| Attention problems | | | |
| r | 0.05 | 0.11 | 0.08 |
| P | 0.305 | 0.020 | 0.025 |
| Aggressive behavior | | | |
| r | 0.12 | 0.19 | 0.15 |
| P | 0.020 | 0.000 | 0.000 |
| Rule breaking | | | |
| r | 0.37 | 0.26 | 0.33 |
| P | 0.000 | 0.000 | 0.000 |
| Intrusive | | | |
| r | 0.16 | 0.21 | 0.18 |
| P | 0.001 | 0.000 | 0.000 |
| Other problems | | | |
| r | 0.11 | 0.11 | 0.12 |
| P | 0.025 | 0.016 | 0.001 |
| Critical items | | | |
| r | 0.27 | 0.16 | 0.23 |
| P | 0.000 | 0.001 | 0.000 |
| Internalizing | | | |
| r | 0.01 | 0.07 | 0.04 |
| P | 0.895 | 0.121 | 0.271 |
| Externalizing | | | |
| r | 0.27 | 0.28 | 0.27 |
| P | 0.000 | 0.000 | 0.000 |

Correlation analyses with sex and age as covariates in all subjects, and with age as a covariate in men/women separately. PC1, the first principal component obtained of principal component analyses of all drinking measures; ASR, Achenbach Adult Self-Report.


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**Table S4** Correlation of hypothalamus-PCL rsFC and ASR measures

| Characteristic | Men (n=406) | Women (n=464) | All (n=870) |
|---|---|---|---|
| Anxious/depressive | | | |
| r | 0.03 | −0.01 | 0.01 |
| P | 0.535 | 0.908 | 0.718 |
| Withdrawn | | | |
| r | −0.00 | −0.00 | −0.01 |
| P | 0.933 | 0.929 | 0.884 |
| Somatic complaints | | | |
| r | 0.05 | 0.04 | 0.04 |
| P | 0.275 | 0.402 | 0.192 |
| Thought problems | | | |
| r | 0.03 | 0.03 | 0.03 |
| P | 0.521 | 0.595 | 0.453 |
| Attention problems | | | |
| r | 0.05 | −0.03 | 0.01 |
| P | 0.275 | 0.492 | 0.721 |
| Aggressive behavior | | | |
| r | 0.03 | 0.05 | 0.04 |
| P | 0.503 | 0.278 | 0.232 |
| Rule breaking | | | |
| r | 0.15 | −0.01 | 0.09 |
| P | 0.002 | 0.898 | 0.009 |
| Intrusive | | | |
| r | 0.03 | 0.07 | 0.05 |
| P | 0.562 | 0.119 | 0.149 |
| Other problems | | | |
| r | 0.02 | 0.06 | 0.03 |
| P | 0.709 | 0.239 | 0.331 |
| Critical items | | | |
| r | 0.06 | −0.02 | 0.02 |
| P | 0.222 | 0.682 | 0.497 |
| Internalizing | | | |
| r | 0.03 | 0.01 | 0.02 |
| P | 0.506 | 0.848 | 0.552 |
| Externalizing | | | |
| r | 0.09 | 0.05 | 0.07 |
| P | 0.060 | 0.275 | 0.029 |

Correlation analyses with sex and age as covariates in all subjects, and with age as a covariate in men/women separately. PCL, paracentral lobule; rsFC, resting state functional connectivity; ASR, Achenbach Adult Self-Report.


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**Table S5** Correlation of hypothalamus-left TPJ rsFC and ASR measures

| Characteristic | Men (n=406) | Women (n=464) | All (n=870) |
|---|---|---|---|
| Anxious/depressive | | | |
| r | −0.03 | 0.03 | −0.01 |
| P | 0.504 | 0.588 | 0.863 |
| Withdrawn | | | |
| r | −0.05 | 0.02 | −0.02 |
| P | 0.346 | 0.616 | 0.627 |
| Somatic complaints | | | |
| r | −0.05 | −0.03 | −0.04 |
| P | 0.345 | 0.589 | 0.274 |
| Thought problems | | | |
| r | −0.02 | −0.06 | −0.04 |
| P | 0.726 | 0.212 | 0.249 |
| Attention problems | | | |
| r | 0.03 | 0.05 | 0.04 |
| P | 0.539 | 0.245 | 0.225 |
| Aggressive behavior | | | |
| r | 0.01 | −0.07 | −0.03 |
| P | 0.895 | 0.129 | 0.375 |
| Rule breaking | | | |
| r | 0.06 | −0.01 | 0.03 |
| P | 0.259 | 0.757 | 0.395 |
| Intrusive | | | |
| r | −0.01 | −0.13 | −0.07 |
| P | 0.794 | 0.006 | 0.055 |
| Other problems | | | |
| r | −0.01 | −0.00 | −0.01 |
| P | 0.918 | 0.939 | 0.842 |
| Critical items | | | |
| r | 0.03 | −0.03 | 0.00 |
| P | 0.578 | 0.574 | 0.944 |
| Internalizing | | | |
| r | −0.05 | 0.01 | −0.02 |
| P | 0.354 | 0.786 | 0.565 |
| Externalizing | | | |
| r | 0.02 | −0.09 | −0.03 |
| P | 0.627 | 0.057 | 0.470 |

Correlation analyses with sex and age as covariates in all subjects, and with age as a covariate in men/women separately. TPJ, temporo-parietal junction; rsFC, resting state functional connectivity; ASR, Achenbach Adult Self-Report.


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