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9   **Title:** An Integrated Multimodal Model of Alcohol Use Disorder Generated by Data-Driven Causal

10   Discovery Analysis

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27   **Abstract**

28   **Objective:** Alcohol use disorder (AUD) has high prevalence and adverse societal impacts, but our

29   understanding of the factors driving AUD is hampered by a lack of studies that describe the complex

30   multifactorial mechanisms driving AUD.

31   **Methods:** We used Causal Discovery Analysis (CDA) with data from the Human Connectome Project

32   (HCP; n = 926 [54% female], 22% AUD [37% female]). Our outcome variable was number of AUD

33   symptoms. We applied exploratory factor analysis (EFA) to parse phenotypic measures into underlying

34   constructs, and assessed functional connectivity within 12 resting-state brain networks as an indicator of

35   brain function. We then employed data-driven CDA to generate an integrated model relating phenotypic

36   factors, fMRI network connectivity, and AUD symptom severity.

37   **Results:** EFA extracted 18 factors representing the wide HCP phenotypic space (100 measures). CDA

38   produced an integrated multimodal model, highlighting a limited set of causes of AUD. The model

39   proposed a hierarchy with causal influence propagating from brain function to cognition (fluid/crystalized

40   cognition, language & working memory) to social (agreeableness/social support) to affective/psychiatric

41   function (negative affect, low conscientiousness/attention, externalizing symptoms) and ultimately AUD

42   severity. Every edge in the model was present at $p < .001$, and the SEM model overall provided a good fit

43   (RMSEA = .06, Tucker-Lewis Index = .91).

44   **Conclusions:** Our data-driven model confirmed hypothesized influences of cognitive and affective

45   factors on AUD, while underscoring that traditional addiction models need to be expanded to highlight

46   the importance of social factors, amongst others. Results further demonstrated that it is possible to extract

47   a limited set of causal factors of AUD, which can inform future research aimed at tracking factors that

48   dynamically predict alcohol use trajectories. Lastly, the presented model identified potential treatment

49   targets for AUD, including neuromodulation of the frontoparietal network, cognitive/affective

50   interventions, and social interventions.

51   **Keywords: alcohol use disorder, causal discovery, resting-state fMRI, RDoC, addiction**

52 **1   Introduction**

53   Lifetime incidence of alcohol use disorder (AUD) is as high as 29-30% (1,2), with alcohol use

54 being a leading cause of death [3 million in the United States, (3); 5.3% of all deaths worldwide; (4)].

55 Success rates for quitting drinking in AUD are low [30-40%; (5,6)], which has been attributed to the

56 multi-causality of the mechanisms underlying AUD and the need for more targeted treatments (7).

57 However, the development of targeted interventions for AUD is hampered by a lack of studies

58 investigating multifactorial mechanisms driving AUD.

59   Early theories of addiction maintenance proposed single key mechanisms, such as allostasis (8),

60 or hedonic signaling (9). These early theories have given way to multifactorial models of addiction, such

61 as the "three-stage cycle" model (10), which proposes that negative affect, incentive salience, and

62 executive function are functional domains involved in addiction. There is a great deal of empirical support

63 for the involvement of these three domains. The three domains have been mapped onto corresponding

64 personality profiles that confer addiction risk (11) and have been used to develop a set of proposed

65 neuroclinical assessment tools (12,13) that were successfully applied to AUD (14). However, a three-

66 domain model is far from encompassing the entire phenotypic space that contributes to AUD. The NIMH

67 RDoC (15,16) proposed 23 functional domains underlying psychopathology, recognizing a need for

68 multivariate models that incorporate increasing knowledge of the many functional domains contributing

69 to psychiatric dysfunction. A recent consensus paper on a multivariate assessment approach for addiction,

70 identified another seven "addiction-specific" domains in addition to the RDoC domains (17). Critically, in

71 all of these approaches, the proposed functional domains were identified by expert consensus and

72 therefore might not exactly match the true underlying domains that exist in the data. For example, in an

73 exploratory analysis of a large public dataset, Van Dam et al. (18) derived seven phenotypic factors that

74 only partially mapped onto RDoC domains, but predicted psychiatric distress. A more recent addiction

75 theory (19) identified ten domains contributing to maladaptive decision-making in addiction. A

76 systematic review of neuroimaging studies in addicted populations, implicated the involvement of at least

77 six different neurobiological mechanisms in AUD (20). These recent developments underscore the need

78   for data-driven, multivariate analysis methods capable of fully examining and describing the large

79   phenotypic space underlying addiction, if we are to understand the central question of how multi-causal

80   factors underlie the maintenance and escalation of alcohol use.

81   In the current study, we leveraged the deep behavioral and psychiatric phenotyping (21) and high-

82   resolution neuroimaging data (22) from the Human Connectome Project (HCP) (23). Using data from

83   nearly 1000 participants we first derived a set of data-driven domains underlying the full range of

84   phenotypic functioning measured in the HCP dataset. We extracted whole-brain connectivity metrics

85   from 12 data-derived resting-state fMRI networks (24) to measure individual neurobiological differences.

86   To examine the relationships between fMRI network connectivity, phenotypic domains, and AUD

87   symptom severity, we applied Causal Discovery Analysis (CDA), a class of machine learning techniques

88   that learns causal models from input data. These methods search the enormous set of possible structural

89   models and return a graph representing estimated causal relationships in the data. The particular method

90   we applied, Greedy Fast Causal Inference (25), uses conditional dependence relations to discover when

91   unmeasured variables confound the relationships between measured variables, making this method

92   particularly powerful for real-world data sets that cannot possibly capture every variable of interest. By 1)

93   deriving data-driven domains encompassing the whole phenotypic space measured in HCP, 2) extracting

94   whole-brain network connectivity profiles, and 3) applying CDA to the resulting phenotypic and

95   neurobiological domains, we generated an integrated, multimodal causal model of neurobehavioral

96   factors contributing to AUD symptom severity.

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98   **2   Methods**

99   **2.1   Subjects**

100   We analyzed data from the final release of the WU-Minn Human Connectome Project (n = 1206,

101   aged 22 – 35, 54% female). All subjects provided written informed consent at Washington University.

102   The causal discovery analysis included all subjects who had complete data from all modalities

103   (phenotypic n = 933, resting-state fMRI n = 1085, final n = 926). Subjects with AUD comprised 22% of

104   the included sample, and 37% of subjects with AUD were female. See Table 1 for demographic

105   characteristics of the included sample.

106

107   *Table 1. Demographic characteristics of the final sample (n = 926).*

Demographics	Options	Total N	AUD	Control	AUD - Control Difference
Gender	M	428	128	300	$\chi 2 = 28.74$, $p < .001$
	F	498	76	498	
Race	White	700	166	534	$\chi 2 = 19.56$, $p = .002$
	Black/African-American	130	15	115	
	Asian/Nat. Hawaiian/Other Pacific Islander	57	8	49	
	Other	39	15	24	
Age	Mean	28.84	28.65	28.88	$t(924) = 0.80$, $p = .43$
	Standard Deviation	3.69	3.38	3.74	
AUD Symptoms	0	538			
	1	184			
	2	98			
	3	46			
	4	43			
	5+	17			
AUD Diagnosis	Yes	204			
	No	722			

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110   **2.2   Outcome Measure: AUD Symptom Severity**

111   Subjects were assessed for symptoms of alcohol abuse and dependence using the Semi-Structured

112   Assessment for the Genetics of Alcoholism (SSAGA). Symptom count data were provided for DSM-IV-

113   TR alcohol abuse and alcohol dependence. Symptom counts for alcohol abuse were provided as 0, 1, or

114   2+, and symptom counts for alcohol dependence were provided as 0, 1, 2, or 3+ (i.e. truncated symptom

115   counts were provided). Given the low number of subjects with the highest symptom counts, it is unlikely

116 that including a more fine-grained symptom count would have provided much additional information. It is

117 therefore also likely that participants mostly had mild/moderate AUD severity, and that as the sample was

118 young adults (age 22-35), this sample likely represents an early stage of AUD.

119 DSM-5 re-categorized alcohol abuse and alcohol dependence into a single disorder (AUD) using

120 the criteria of both alcohol abuse and dependence, with one symptom of alcohol abuse removed (legal

121 problems) and one symptom added (craving). We reconstructed this change by adding alcohol abuse and

122 dependence symptom counts for each subject. Given recent interest in dimensional rather than categorical

123 psychiatric dysfunction, we used the AUD symptom count (severity) as our primary outcome variable.

124 **2.3   Behavioral and Self-Report Measures**

125 The HCP dataset contains a wide array of self-report, diagnostic and behavioral measures

126 assessing domains of cognition, emotion, social function, psychiatric dysfunction, and personality. We

127 selected all available measures from these domains for further analysis (100 in total). We included all

128 provided measures, but when provided, we used summary scores rather than item-level or minor scores as

129 long as the summary score encompassed the task construct of interest (26). For example, for the Short

130 Continuous Penn Test, we included the summary statistics of sensitivity and specificity but not more

131 specific scores, and for delay discounting we included the area under the curve for $200 and $40k but not

132 the individual discounting levels. For in-scanner tasks, we included a separate measure for each of the

133 major conditions. If both age/gender-adjusted and unadjusted scores were provided, we included only the

134 adjusted scores. We also excluded all items that were linear combinations of other data. For a list of

135 included variables and excluded variables and descriptive statistics of the included variables see the

136 Supplement.

137 **2.4   Factor Analysis of Phenotypic Data**

138 To reduce the phenotypic space measured in the Human Connectome Project to a set of

139 underlying domains, we conducted an exploratory factor analysis (maximum likelihood factor extraction,

140 oblimin rotation to allow for correlated factors) in the entire HCP sample that had complete phenotypic

141 data (n = 933, 53.5% female). EFA was calculated in R using the 'psych' package (27). The choice of

142   EFA over similar data reduction schemes such as PCA was made because EFA explicitly accounts for

143   error due to unreliability in measurement (28) unlike PCA (29). Oblimin rotation allows for correlated

144   factors, which is critical to data reduction over a large phenotypic variable space as we expect many

145   factors to be closely related but separable (for example, negative affect and internalizing

146   psychopathology). We used Monte Carlo permutation analysis (parallel analysis) (30) to determine how

147   many factors were statistically significant at $p < .05$ (31). Monte Carlo simulation was also calculated

148   using the 'psych' package for R (27).

149   **2.5   Resting-State fMRI Acquisition and Preprocessing**

150   High-resolution structural and functional MRI data were collected on a Siemens 3T Connectome

151   Skyra scanner with a 32-channel head coil at Washington University. See Uğurbil et al. (22) for a full

152   description of the acquisition parameters for rfMRI in the HCP database. Structural data were

153   preprocessed as described in Glasser et al. (32), using the most recent version of the HCP preprocessing

154   pipeline (4.1). Briefly, anatomical image preprocessing consisted of bias field and gradient distortion

155   correction, coregistration of T1w and T2w images, and linear and nonlinear registration to MNI space.

156   Cortical surfaces were constructed using FreeSurfer. Surface files were transformed to MNI space,

157   registered to the individual's native-mesh surfaces, and downsampled.

158   Functional MRI preprocessing is fully described in Glasser et al. (32). Briefly, volumetric fMRI

159   were subjected to gradient distortion correction, motion correction, and referencing to T1w. All

160   transforms were concatenated and run in a single nonlinear resampling to MNI space. Data were then

161   masked by the PostFreeSurfer brain mask and normalized. This volumetric timeseries was then mapped to

162   a combined cortical surface and subcortical voxel space ("grayordinates") and smoothed with a 2mm

163   FWHM Gaussian.

164   Finally, fMRI data were high-pass filtered (FWHM = 2355 s) and cleaned of artifacts using ICA-

165   FIX (33,34). Artifact components and 24 motion regressors (35) were regressed out of the data in a single

166   step. This produced the final ICA-FIX denoised version of the data

167   (https://www.humanconnectome.org/study/hcp-young-adult/document/1200-subjects-data-release) that

168   we used for all analyses.

169   **2.6   rfMRI Parcellation and Network Assignment**

170   We parcellated the whole brain, including cortex, subcortex, and cerebellum, into 718 parcels

171   using the Cole-Antecevic parcellation (24), a parcellation scheme that builds on the Glasser et al. (36)

172   multimodal cortex parcellation (360 parcels). We chose the Cole-Antecevic parcellation because while

173   the Glasser parcellation used multiple measures including myelination, rfMRI activity, and anatomical

174   landmarks to delineate a fine-grained map of cortical space, it did not include any subcortical voxels, and

175   did not explicitly assign parcels to large-scale networks using principled statistical methods. The Cole-

176   Antecevic parcellation built on the Glasser parcellation by 1) assigning subcortical and cerebellar voxels

177   to parcels, and 2) by using Louvain community detection to delineate 12 large-scale networks consisting

178   of cortical, subcortical, and cerebellar regions.

179   **2.7   Calculation of rfMRI Network Connectivity**

180   For each of the 12 data-derived networks, we computed pairwise Pearson correlations between

181   each pair of parcels in the network. Pearson correlations were transformed to approximate a normal

182   distribution using Fisher's z-transform. Within each of the 12 networks, we then took the average of the

183   parcel-to-parcel correlations to obtain a summary statistic for within-network connectivity (37–41). This

184   procedure therefore summarizes how tightly connected (coherent) the regions comprising each of the 12

185   networks are with each other. This resulted in 12 average network-level connectivity values for each

186   subject. Figure 1 contains a graphical depiction of whole-brain network assignments.

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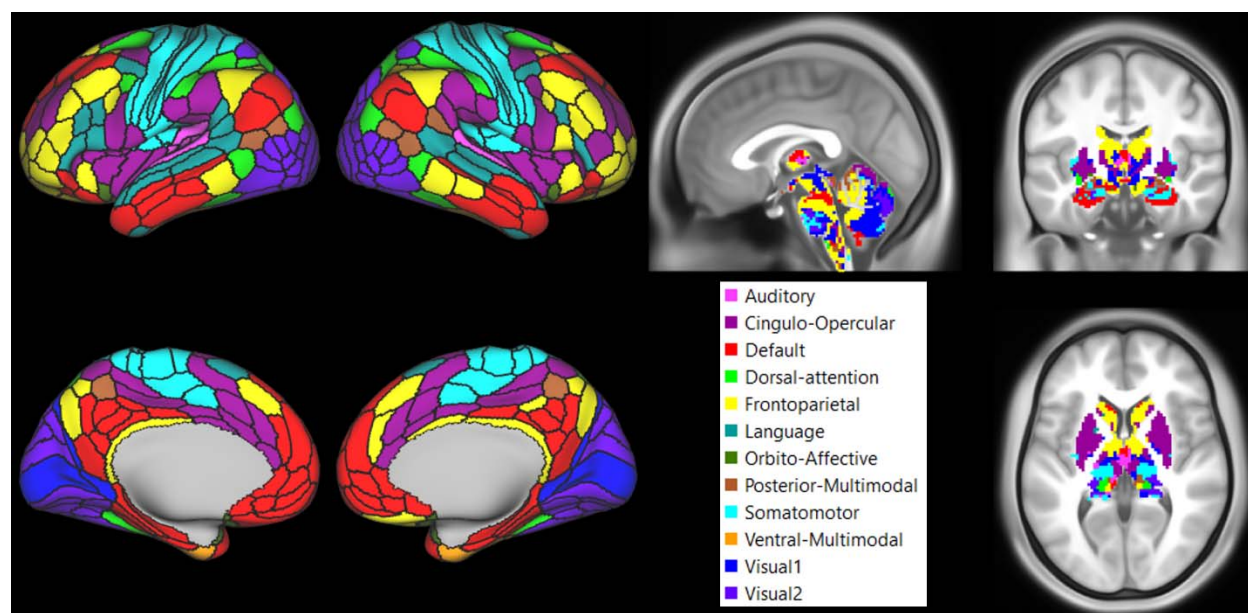
189   *Figure 1. We conducted a whole-brain parcellation and assigned brain parcels to 12 large-scale*

190   *networks according to the Cole-Antecevic Parcellation (24). This parcellation built on the Glasser*

191   *multimodal cortical parcellation by including subcortical and cerebellar parcels, and assigned each of*

192   *the 718 parcels to a large-scale brain network using Louvain community detection.*

193

194   **2.8   Causal Discovery Analysis: Greedy Fast Causal Inference (GFCI)**

195   Causal models represent, often graphically, the set of cause-and-effect relationships that are

196   present within a set of data (42). As the number of variables in a dataset increases, so too does the space

197   of possible causal models that could give rise to the observed data, making the problem of identifying

198   which of the potential causal models best fits the observed data very difficult. Causal Discovery Analysis

199   (CDA) uses machine learning to determine which causal models are best supported by the data (43).

200   There are many CDA algorithms that make a wide variety of assumptions and have varying performance

201   characteristics; for review, see Glymour et al. (44).

202   In the current study, we applied Greedy Fast Causal Inference (GFCI) (25), an accurate and fast

203   algorithm for establishing causal relationships from data even in the presence of unmeasured confounds.

204   GFCI operates in two phases. GFCI begins by searching the space of possible graphs to create a

205   preliminary graph that minimizes a penalized likelihood score, in this case the Bayesian Information

206   Criteria (BIC) (45). This initial search phase is done using the Fast Greedy Equivalence Search method

207   (46). After the initial search phase, the algorithm refines the discovered graph by conducting a series of

208   conditional independence tests. This phase rules out any edges that imply conditional dependencies not

209   borne out by the data (for an example, see *Figure 2*). The most important distinction of GFCI compared to

210   other causal discovery methods is that GFCI can detect confounding factors, and as such is particularly

211   suited to analysis of real-world data, where there is no guarantee that every relevant variable has been

212   measured. The output of the GFCI algorithm is a partial ancestral graph with edge types indicating causal

213   relationships, uncertain relationships, and the presence of unmeasured confounding variables.

214   GFCI analysis was implemented using Tetrad v6.7, running in Java. Analysis was run with

215   default parameters; that is, using alpha = .01, maximum degree of the graph = 100, and a penalty discount

216   of two. Penalized likelihoods for models were calculated using the Bayesian Information Criteria (45),

217   which is the default model fit index in Tetrad and the most commonly used model fit index in CDA. To

218   recover effect sizes of the edges in the model, we fit a structural equation model (SEM) to the graph

219   structure using the 'lavaan' package for R (47). We present the graph GFCI learned from the full dataset

220   with SEM effect sizes for each edge. As an additional analysis of model stability in smaller samples, we

221   also conducted a stability analysis by resampling 90% of the sample (48) without replacement with 2000

222   repetitions (jackknifing); the resampling stability of each edge is presented in the Supplement.

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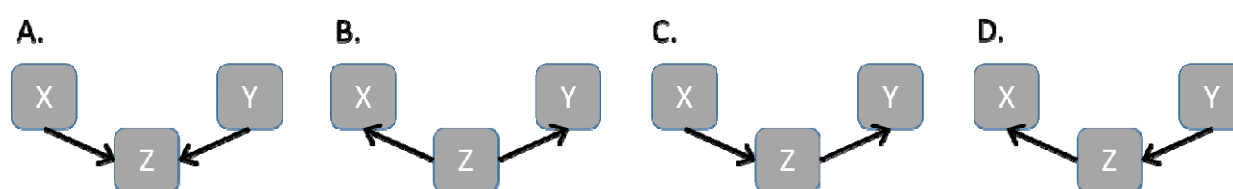
225   *Figure 2. Four different ways that three variables X, Y, and Z could be causally related. Panel A is a*

226   *structure known as a "collider," in which X and Y both cause Z, but X and Y are not related. In this*

227   *structure, X and Z are dependent, and Y and Z are dependent, while X and Y are independent. However,*

228   *when Z is conditioned on (controlled for), X and Y are dependent. Meanwhile, in panel **B**, Z causes both*

229   *X and Y. In this structure, X and Y are dependent because of their common cause, and are independent*

230   *when Z is conditioned on. In Panels **C & D**, X and Y are dependent because one causes Z, which then*

231   *causes the other. In both of these panels, X and Y are independent when Z is conditioned on, as Z is the*

232   *only link from X to Y. GFCI utilizes conditional independence tests to determine causal direction in graph*

233   *edges, specifically by identifying "collider" cases in the graph (since these cases imply different*

234   *conditional dependencies than the other three cases).*

235

236   **3   Results**

237   **3.1   Exploratory Factor Analysis: Decomposing the Phenotypic Space of the HCP**

238   Based on the results of Monte Carlo simulation we extracted 18 factors ($p < .05$) from the 100-

239   variable space, which collectively accounted for 47% of common variance. Factor loadings for each item

240   are described in the Supplement. Results of the Monte Carlo permutation test for eigenvalue significance,

241   and percent variance explained per factor, eigenvalues, and cumulative variance are presented in the

242   Supplement. EFA model fit indices indicated good factor separation (RMSEA = .03, Tucker-Lewis Index

243   = .86).

244   Factors, in order of common variance accounted for, were associated with: 1) Somaticism (high

245   DSM/ASR somaticism, high DSM depression, low PSQI sleep quality), 2) Fluid Cognition (high Raven's

246   progressive matrices performance), 3) Internalizing (high DSM/ASR anxiety, high DSM depression, high

247   NEO-FFI neuroticism), 4) Gambling Task Reaction Time (slow gambling task reaction time), 5)

248   Conscientiousness/Attention (low DSM ADHD, low ASR attention problems, and high NEO-FFI

249   conscientiousness), 6) Visuospatial Processing (high Penn short line orientation task performance), 7)

250   Social Support (high NIH toolbox friendship, low loneliness, low perceived rejection and perceived

251   hostility, high emotional and instrumental support), 8) Processing Speed (high NIH toolbox flanker total

252   score, fast fMRI emotion task RT), 9) Externalizing (high ASR aggression and rule-breaking, high DSM

253   antisocial, high NIH toolbox aggression), 10) Social Withdrawal (high ASR withdrawal, high DSM

254 avoidance, low NEO-FFI extraversion), 11) Language Task Performance (high fMRI language task story

255 average difficulty, and high math problem accuracy), 12) Relational Task Reaction Time (slow fMRI

256 relational task RT), 13) Delay Discounting (high delay discounting AUC for $200 and $40k), 14)

257 Memory Performance (fMRI N-Back task fast RT and high accuracy, fast Penn word memory RT), 15)

258 Negative Affect (high NIH toolbox anger, fear, sadness and stress), 16) Crystalized IQ (high NIH toolbox

259 English reading and picture vocabulary, high education, and high NEO-FFI openness), 17) Positive Affect

260 (high NIH toolbox life satisfaction, positive affect, and meaning and purpose, and NEO-FFI

261 extraversion), and 18) Agreeableness (low aggression and high NEO-FFI agreeableness).

262 **3.2 Causal Discovery of the Neurobehavioral Underpinnings of Alcohol Use Disorder**

263 The output of GFCI is presented in *Figure 3*. The SEM fit to this model indicated a good fit,

264 RMSEA = .06, Tucker-Lewis Index = .91. Recovered edge weights from SEM were presented overlaid on

265 the GFCI graph. Jacknife testing demonstrated the stability of the model (2000 repetitions; see

266 Supplement).

267 First, we found that brain network connectivity measures and phenotypic factors largely separated

268 into two interconnected separate clusters. The brain network subgraph indicated several salient points. We

269 found that high connectivity within the language network during rest caused high connectivity within

270 default mode (DMN), cingulo-opercular, and multi-modal sensory association networks - networks that

271 play a central role in self-reflective brain processes. We also found effects indicating causal influences of

272 cingulo-opercular connectivity on attentional processing (cingulo-opercular -> dorsal attention). Finally,

273 we found converging causal influences onto the frontoparietal network (cingulo-opercular/posterior

274 multimodal -> frontoparietal, dorsal attention -> frontoparietal).

275 Brain connectivity intersected with behavioral phenotypic variables in a link between high

276 frontoparietal connectivity and high Fluid Cognition. From this point, causal influences propagated from

277 Fluid Cognition to Visuospatial Processing and Crystalized IQ, replicating a well-studied effect that

278 individuals high in fluid cognitive ability will also be high in crystalized intelligence (49,50). From there

279 causal influences proceeded to more specific cognitive measures, including Working Memory, Language

280   Task Performance and Delay Discounting. We found a direct link between Crystalized IQ and Delay

281   Discounting, such that individuals higher in Crystalized IQ also exhibited lower (less impulsive)

282   discounting rates. These cognitive measures were then in turn causally linked to affective, social and

283   psychiatric factors. High Language Task performance and less impulsive Delay Discounting caused

284   Agreeableness. Low Working Memory performance and low Agreeableness caused lowered Social

285   Support, and decreased Social Support contributed to increased Negative Affect, increased Social

286   Withdrawal, and decreased Positive Affect. High Negative Affect in turn contributed to higher

287   Internalizing symptoms, and lower Conscientiousness/Attention. Low Conscientiousness/Attention and

288   low Agreeableness caused high Externalizing psychopathology, while high Externalizing

289   psychopathology directly caused increased AUD symptom severity.

290   Previous hypotheses have particularly focused on the influences of negative affect, incentive

291   salience, and executive function in AUD. Our results support a causal role for cognitive and affective

292   influences on AUD, while expanding our understanding of the complex multifactorial space contributing
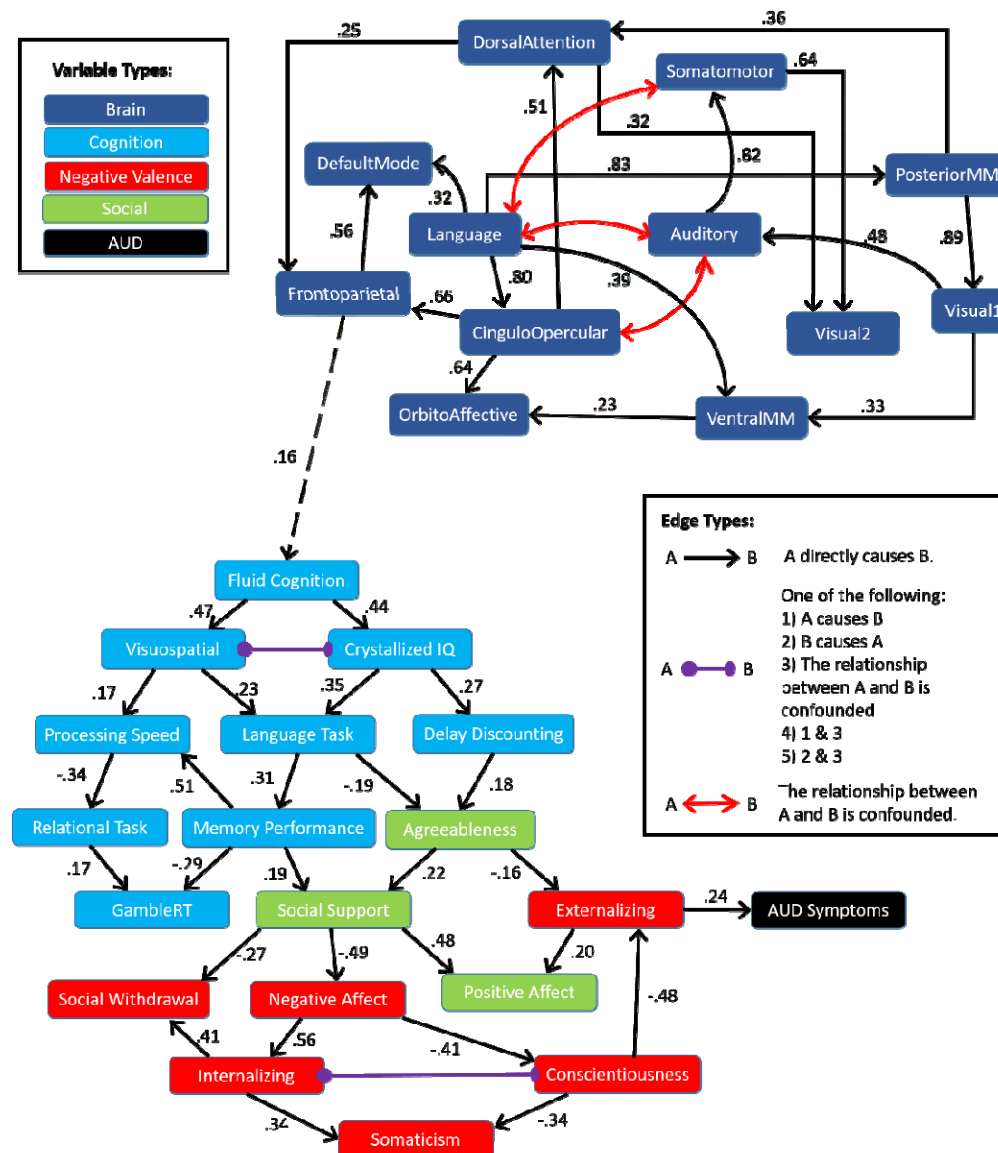
293   to AUD.

294

295

Figure 3. Causal Discovery Analysis of the neurobehavioral determinants of AUD symptom severity in

the HCP dataset was done using Greedy Fast Causal Inference (GFCI). GFCI returns a partial ancestral

graph (PAG) depicting causal relationships between a set of variables, while assessing for unmeasured

third variables in relationships (confounders). Standardized edge weights recovered via SEM are

displayed in text next to each edge in the graph.

301

4   Discussion

303   Early addiction models posited that addiction was due to single key mechanisms (8,9), but

304   modern addiction models have begun to emphasize the multifactorial mechanisms underlying addiction

305   (10,12,17,19,20). In this study, we used a data-driven approach to characterize phenotypic domains in a

306   large community sample, and examined whole-brain network connectivity at a large scale using a data-

307   driven network analysis and parcellation (24). We then modeled large-scale brain and behavioral

308   influences on alcohol use disorder (AUD) symptom severity using causal discovery analysis. Our results

309   shed light on the relationship between brain network connectivity and phenotypic domains in general, as

310   well as providing specific information on how brain and behavioral factors contribute to the severity of

311   AUD, and which could be targeted in treatment.

312   **4.1   Expanding the Multifactorial Space of Current Addiction Models**

313   Our factor analysis uncovered a variety of factors that map relatively well onto domains

314   elaborated in RDoC (*Table 2*). For example, we found factors that mapped well onto aspects of the RDoC

315   Cognitive Systems domain, the RDoC Negative Valence Systems domain, and the RDoC Social domain.

316   To assist in interpreting the large-scale domains that our data-driven factors mapped onto, we grouped

317   factors based on their correlations. Interestingly, we found that the Conscientiousness/Attention and the

318   Social Withdrawal factors correlated with other factors in the Negative Valence Systems domain, rather

319   than the RDoC-assigned grouping of these factors (Cognitive Systems: Attention, and Social Systems:

320   Affiliation & Attachment, respectively). A previous review found that inattention and anxiety are tightly

321   linked (51) but our results provide evidence of the direct link between inattention and negative affect. We

322   also found that the Delay Discounting factor, while considered part of the RDoC Positive Valence

323   System: Reward Valuation subconstruct (52), correlated instead with Cognitive Systems factors,

324   suggesting delay discounting is more related to Cognitive Control/Impulsivity domains than to Reward

325   Valuation (53–55).

326

327   *Table 2. Discovered factors (EFA) using 100 phenotypic measures. Factors are grouped according to*

328   *correlations between the factors. The right column indicates the RDoC domain each factor most closely*

329   *approximated. Factors whose correlation structure did not match the RDoC domain assignment for that*

330   *factor (n = 3) are displayed in red.*

Domains	Factors grouped according to factor correlations	RDoC subdomains (**non-fitting marked in red**)
Negative Valence	Externalizing (high ASR aggression and rule-breaking, high DSM antisocial, high NIH aggression)	Frustrative Non-Reward
	Conscientiousness/Attention (low DSM ADHD, low ASR attention problems, and high NEO-FFI conscientiousness)	Attention
	Somaticism (high DSM/ASR somaticism, high DSM depression, low PSQI sleep quality)	Sustained Threat
	Internalizing (high DSM/ASR anxiety, high DSM depression, high NEO-FFI neuroticism)	Potential Threat, Sustained Threat
	Negative Affect (high NIH anger, fear, sadness and stress)	Acute Threat, Loss, Sustained Threat
	Social Withdrawal (high ASR withdrawal, high DSM avoidance, low NEO-FFI extraversion)	Affiliation & Attachment
Cognition	Visuospatial Processing (high Penn short line orientation task performance)	Visual
	Delay Discounting (high delay discounting AUC for $200 and $40k)	Reward Valuation
	Language Task Performance (high fMRI language task story average difficulty, and high math problem accuracy)	Language Behavior
	Crystalized IQ (high NIH English reading and picture vocabulary, high education, and high NEO-FFI openness)	Declarative Memory
	Fluid Cognition (high Raven's progressive matrices performance)	Working memory
	Gambling Task Reaction Time (slow gambling task reaction time)	
	Memory Performance (fMRI N-Back task fast RT and high accuracy, fast Penn word memory RT)	Declarative/Working Memory
	Processing Speed (high NIH flanker total score, fast fMRI emotion task RT)	
	Relational Task Reaction Time (slow fMRI relational task RT)	
Social	Social Support (high NIH friendship, low loneliness, low perceived rejection and perceived hostility, high emotional and instrumental support)	Affiliation and Attachment
	Positive Affect (high NIH life satisfaction, positive affect, and meaning and purpose, and NEO-FFI extraversion)	Perception and Self
	Agreeableness (low aggression and high NEO-FFI agreeableness)	Affiliation and Attachment

331

332

333   Here we summarize several key points from our mapping of causal influences on AUD symptom

334   severity onto the RDoC framework. First, our analysis uncovered strong evidence for the direct causal

335   effect of the Negative Valence domain in AUD. This specifically included a causal influence of the

336   Negative Affect factor on AUD, mediated through Conscientiousness/Attention (which correlated with

337   other Negative Valence Systems factors). While many neurobiological models of addiction agree on the

338   importance of negative affect in AUD (10,20), this is not unanimously agreed upon by experts in the

339   addiction sciences (17). The presented empirical data hence provides important empirical evidence

340   implicating the broader Negative Affect Domain (as defined in RDoC) as an important treatment target in

341   AUD.

342   Second, our analysis uncovered strong evidence for a mediating/buffering role of the Social

343   Systems domain in AUD. Low Social Support and low Agreeableness were indirect causes of AUD

344   severity and fully mediated the effect of cognition on the negative valence domain, providing strong

345   empirical evidence that addiction models should incorporate measures of social function (56,57).

346   Epidemiological research has established a solid link between social affiliation and drug addiction (58),

347   and increased social affiliation is associated with decreased risk of relapse in drug users who are seeking

348   treatment (59). Despite the considerable evidence research has uncovered for the importance of social

349   affiliation as a protective factor in addiction (60), current neurobiological models of addiction generally

350   fail to consider social factors (56) and their close relationship to cognitive/affective factors.

351   We generally found weak evidence for the involvement of the Positive Valence Systems domain

352   in this analysis, although this is likely due to a limitation of the dataset employed. Positive Valence

353   Systems subdomains, including reward-based domains that are particularly important in addiction (17) are

354   relatively neglected in the HCP dataset (61). We did find a causal influence of Delay Discounting on

355   AUD severity, but as noted previously the Delay Discounting factor correlated with other Cognitive

356   factors, suggesting that Delay Discounting (as measured in the HCP study) might be related to Cognitive

357   Control/Impulsivity more so than Reward Valuation (53–55).

358   Finally, our analysis provides strong evidence that prefrontal cortex (PFC) brain networks, and

359   associated cognitive factors, are situated at the top of the causal hierarchy of influences on AUD severity.

360   The role of prefrontal cortex and associated high-level cognitive factors in addiction is often referenced

361   and is a part of major current theories of addiction (20,62), but our results are among the first to

362   empirically demonstrate this hierarchical influence on AUD. Importantly, our causal model indicates that

363   cognitive influences on AUD severity may extend far beyond the traditional consensus that inhibitory

364   control is the most important cognitive influence on addiction (17,62,63), as we also highlighted

365   influences of fluid and Crystallized IQ, working memory, and language on AUD.

366   **4.2   Impact of Results on Theorized Externalizing and Internalizing Pathways to AUD**

367   Previous research has shown that externalizing symptomatology predicts AUD in young adult

368   samples (64). Our data-driven causal model revealed that externalizing fully mediated the impact of all

369   other (measured) causes of AUD; that is, AUD is unrelated to other phenotypic or brain network factors

370   when externalizing is controlled for. Note that our externalizing factor consisted of ASR rule-breaking,

371   aggression, and antisocial scales, and NIH toolbox aggression. The ASR rule-breaking scale contains an

372   item that assesses whether a subject "gets drunk," but this does not appear to have influenced the current

373   analysis. First, this is only one out of 14 items on the rule-breaking scale (and 40 items in total that

374   contributed to the Externalizing factor). Second, all four scales that formed the Externalizing factor

375   independently correlated with AUD symptom severity (all $p < .001$), such that each individual aspect of

376   Externalizing appears to be related to AUD severity. Overall the model hence supports that externalizing

377   symptoms in general mediate the causal influence of other factors on AUD.

378   Research has also focused on the high coincidence of AUD and internalizing disorders (65–67).

379   Previous causal modeling research found a causal path from internalizing disorder to drinking behavior in

380   AUD (mediated through drinking-to-cope) (68). The current model contains a confounded relationship

381   between Internalizing and Conscientiousness/Attention, indicating an inability of the model to determine

382   the relationship between these two factors, possibly due to underlying constructs (e.g. drinking motives)

383   that were not captured in this data set. Therefore, it remains to be further described by future research if

384   negative affect is a common underlying cause of internalizing and AUD symptoms (65), or if there is an

385   independent causal influence of internalizing psychopathology on AUD symptoms. It is possible that this

386   relationship could be better examined through a longitudinal study, as pathodevelopmental perspectives

387   on AUD have proposed that early stages of addiction are characterized by low levels of internalizing, but

388   later stages of addiction are characterized by increasing levels of internalizing (65).

389   **4.3   A Gray Area in the Literature – the Role of Fluid Cognition in AUD**

390   Executive function is central to neurobiological models of addiction (10,20,62,63). Fluid

391   cognition (here, measured through performance on an abbreviated form of Raven's progressive matrices)

392   (69), or a person's ability to reason and think abstractly and flexibly, has an intuitive relationship with the

393   concept of executive function. Authors have often considered working memory to be either indicative of

394   executive function (70), or of fluid cognition (71), and executive function and fluid cognition are

395   similarly impacted by brain lesions (72). Our results generate the hypothesis that fluid cognition and

396   Crystalized IQ, including problem-solving and abstract reasoning, lie at the beginning of a causal

397   hierarchy eventually influencing AUD severity. This fits previous empirical evidence demonstrating that

398   AUD is associated with deficits attributed to various fluid cognitive abilities or executive function such as

399   working memory (73,74) and planning and goal maintenance (75), but expands on this by indicating that

400   these factors have a causal influence on AUD symptom severity. Previous research has also demonstrated

401   that high-level cognition predicts initiation of substance use in adolescence (76), lifetime drug use and

402   abuse (77) and addiction treatment outcomes (78). Our model thus adds to the growing body of empirical

403   evidence that proposes a causal role of cognition as a primary resilience factor and potential treatment

404   target in AUD.

405   **4.4   Brain Network Influences in AUD**

406   We found a direct brain-phenotype link from frontoparietal (executive) network connectivity to

407   fluid cognition, corroborating previous evidence of this link in healthy populations (79–83). In addiction,

408   frontoparietal network dysfunction has been implicated in impaired inhibitory control (20,84,85) and self-

409   regulation (51,85). Individuals with AUD show decreased recruitment of frontoparietal network during

410   social-emotional processing (86,87), decision-making (88), and cognitive control (89), as well as

411   decreased frontoparietal connectivity during rest (90). Frontoparietal disengagement during social-

412   emotional processing predicts relapse in AUD (91), and decreased frontoparietal activation during

413   inhibitory control predicts later drinking in adolescents (92,93). Our results indicate that causal influences

414   of frontoparietal network connectivity on AUD are mediated through deficits in overall cognitive ability

415   and its downstream effects on the broader Negative Affect domain. A recent systematic review (94) also

416   showed that targeting dlPFC (part of the frontoparietal network) (24) can improve cognitive deficits in

417   addiction, including executive functions. This is particularly relevant, as our data-driven model also

418   indicates that neuromodulation of frontoparietal network could improve executive functioning, with

419   downstream effects on AUD severity.

420   We also found direct effects of cingulo-opercular and dorsal attention network connectivity onto

421   the frontoparietal network. The Cingulo-opercular network reacts to salient stimuli regardless of

422   positive/negative valence (95,96), while the dorsal attention network supports the external focusing of

423   attention (97) and encodes top-down control and working memory load (98). Individuals with AUD also

424   show decreased cingulo-opercular activation during social-emotional processing (86,87), cognitive

425   control (89,99,100), and decision-making (88). Our results suggest that dysfunctional connectivity in

426   salience and attentional networks can contribute to cognitive dysfunction in AUD, with these effects

427   being mediated through executive network connectivity. The presented causal model hence provides

428   direct evidence for brain-directed treatment approaches targeted at the frontoparietal network, such as

429   cognition-enhancing therapy (85,101,102), pharmacological interventions (cognitive enhancers) (101) or

430   neuromodulation treatment (e.g., by external devices) (94,103) or neurofeedback interventions (51).

431   A novel result generated from our causal discovery analysis is the role of language network

432   connectivity as a central "hub" in the brain during resting-state. Language network connectivity caused

433   cingulo-opercular network connectivity directly, and indirectly caused dorsal attention network

434   connectivity (mediated through cingulo-opercular connectivity, and posterior multi-modal association

435   network connectivity). Therefore, language network connectivity exerts influences on frontoparietal

436   network connectivity through multiple different pathways, and might have long-range impacts on

437   cognition and eventually on AUD severity. The potential involvement of language network in AUD

438   appears to have been scarcely investigated. This network encompasses vlPFC regions that are close to left

439   dlPFC regions that are often targeted in neuromodulation interventions for addiction (103), and therefore

440   neuromodulation targeted at left DLPFC might also stimulate language networks. Left vlPFC regions are

441   also implicated in cognitive interventions for addiction (85). Future analysis should examine the

442   relationship between brain language networks and cognitive dysfunction in AUD, and the implications for

443   treatment.

4.6   Limitations

445   The analysis method used in the current manuscript is not free of limitations, and other limitations

446   are also imposed by the nature of the dataset we used. Notably, the fact that we did not find any cycles

447   (i.e. variable X causes variable Y, and variable Y causes variable X) in the current data does not mean

448   that they do not exist. The causal discovery algorithm used in this analysis cannot discover recurring

449   cycles in cross-sectional data, but is capable of discovering recurrent cycles when more than one time

450   point is measured and the cycles unfold over time. Future analysis should incorporate longitudinal data to

451   specifically test the possibility that recurrent cycles might contribute to AUD (10). This limitation extends

452   to the brain network subgraph we recovered as well; the causal discovery algorithm we used cannot

453   recover bidirectional relationships in cross-sectional data, so some brain network links that are actually

454   bidirectional processing streams may instead be represented as the predominant causal relationship

455   between two networks. Finally, the CDA algorithm also uses a penalized likelihood score, therefore

456   potentially missing weak causal links present in the data; however, this practice also serves to increase the

457   confidence in the causal relationships the algorithm does find.

458   An important limitation of the data set is the extremely limited assessment of the Positive

459   Valence domain in the HCP dataset. Current perspectives in addiction emphasize the role of Positive

460   Valence domains (10,17,20,62,63), but the HCP dataset does not contain many measures in this domain.

461   The data did contain a measure of Delay Discounting, which had causal influences on AUD severity, but

462   this factor appeared to be grouped with other cognitive factors and could not be interpreted as a unique

463   measure of Reward Valuation. The HCP dataset also contained a gambling choice fMRI task, but this task

464   did not provide a phenotypic measure of incentive salience processing. Future analysis will need to

465   carefully measure Positive Valence domains, in addition to the domains measured in the HCP dataset, to

466   determine where these domains fit in an overall causal model of AUD. Another limitation of the dataset is

467   that the cross-sectional design employed by the HCP is also unable to assess certain predictions of

468 pathodevelopmental perspectives on addiction, such as the possibility that different causal factors are

469 involved in early and late stages of AUD (65).

4.6   Conclusions

471   This study is the first to conduct a machine learning search for causal influences of AUD

472 symptoms over a wide phenotypic and neurobiological space. We found phenotypic factors related to

473 several RDoC domains, and confirmed hypothesized influences of a Negative Valence (Negative affect >

474 Conscientiousness/Inattention > Externalizing > AUD symptom severity), and Cognitive Systems (Fluid

475 Cognition > Crystalized IQ > Working Memory/Language> Social/Affective/Psychiatric factors > AUD

476 symptom severity) on AUD. The model proposed a hierarchy with causal influence propagating from

477 brain function to cognition (Fluid/Crystalized Cognition, Language & Working Memory) to social

478 (Agreeableness/Social Support) to affective/psychiatric function (Negative Affect, low

479 Conscientiousness/Attention, Externalizing symptoms) and ultimately AUD symptoms. These results

480 underscore a) a strong causal link between prefrontal brain function/cognition and affective/psychiatric

481 factors and b) an important buffer function of social factors (Social Support, Agreeableness). Our data-

482 driven model hence confirmed hypothesized influences of cognitive and affective factors on AUD, while

483 underscoring that traditional addiction models need to be expanded to highlight the importance of social

484 factors, amongst others. Results further demonstrated that it is possible to reduce a broad phenotypic

485 space (100 measures) to a limited set of causal factors of AUD, which can inform future research. We

486 argue that the presented causal model of AUD provides evidence for exploring two different kinds of

487 treatment approaches, specifically for investigating a) "top-down" interventions aimed at enhancing high-

488 level cognition, including brain-directed interventions targeting the executive network and b)

489 "integrative" interventions that take the interplay between brain/cognitive, affective/psychiatric factors

490 and social factors into account. We note that we did not investigate the individual heterogeneity of the

491 causal factors involved in this model, but only provided a static causal model of an "average" individual

492 with AUD symptoms, as a first step. We believe that this initial step of describing a comprehensive,

493 integrated, multimodal but also reduced model (in a principled data-driven way) is crucial. We see the

494   provided causal model as a working model, which can be further expanded (e.g. by the RDoC Positive

495   Valence factors), explored with regards to individual heterogeneity and used in predictive modelling

496   studies on alcohol use trajectories in active users, as well as in individuals with AUD in treatment.

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505   The authors report no biomedical financial interests or potential conflicts of interest.

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