Research Paper

Elevated decision uncertainty and reduced avoidance drives in depression, anxiety and substance use disorders during approach–avoidance conflict: a replication study

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Background: Decision-making under approach–avoidance conflict (AAC; e.g., sacrificing quality of life to avoid feared outcomes) may be affected in multiple psychiatric disorders. Recently, we used a computational (active inference) model to characterize information processing differences during AAC in individuals with depression, anxiety and/or substance use disorders. Individuals with psychiatric disorders exhibited increased decision uncertainty (DU) and reduced sensitivity to unpleasant stimuli. This preregistered study aimed to determine the replicability of this processing dysfunction. **Methods:** A new sample of participants completed the AAC task. Individual-level computational parameter estimates, reflecting decision uncertainty and sensitivity to unpleasant stimuli ("emotion conflict"; EC), were obtained and compared between groups. Subsequent analyses combining the prior and current samples allowed assessment of narrower disorder categories. **Results:** The sample in the present study included 480 participants: 97 healthy controls, 175 individuals with substance use disorders and 208 individuals with depression and/or anxiety disorders. Individuals with substance use disorders showed higher DU and lower EC values than healthy controls. The EC values were lower in females, but not males, with depression and/or anxiety disorders than in healthy controls. However, the previously observed difference in DU between participants with depression and/or anxiety disorders and healthy controls did not replicate. Analyses of specific disorders in the combined samples indicated that effects were common across different substance use disorders and affective disorders. **Limitations:** There were differences, although with small effect size, in age and baseline intellectual functioning between the previous and current sample, which may have affected replication of DU differences in participants with depression and/or anxiety disorders. **Conclusion:** The now robust evidence base for these clinical group differences motivates specific questions that should be addressed in future research: can DU and EC become behavioural treatment targets, and can we identify neural substrates of DU and EC that could be used to measure severity of dysfunction or as neuromodulatory treatment targets?

Introduction

Several psychiatric disorders are characterized by maladaptive patterns of behaviour during approach–avoidance conflict (AAC); that is, when both positive and negative outcomes may result from the same choice.[1] This includes maladaptive avoidance behaviours in individuals with depression/anxiety, which are thought to maintain symptoms and are often targeted in psychotherapy,[2] as well as drug-seeking behaviours in those with substance use disorders who sacrifice quality of life to avoid uncomfortable withdrawal states and/or seek out reinforcing sensations or experiences.[3] Understanding the cognitive and computational processes leading to these patterns of maladaptive choice is an important research direction that could point toward novel therapeutic targets.[4]

Various tasks have emerged to investigate the resolution of AAC using computational modelling. This approach can measure distinct information processing mechanisms during decision-making. From a computational perspective, impairments in AAC decision-making might be attributed to a range of mechanisms, including suboptimal reinforcement learning, outcome/action valuation, uncertainty, inference or planning processes, among others. As such, an effective way

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to understand maladaptive choices across clinical populations is empirical application of these models. To this end, recent studies applying this approach have investigated how both initial choice biases and rates of evidence accumulation are associated with depression, threat and their neural basis;[5,6] other studies have highlighted links between outcome value and peripheral physiology, as well as neural correlates of competing action values.[7,8]

In a recent study of AAC behaviour in individuals with depression/anxiety or substance use disorders,[9] we used a Bayesian computational (active inference) model to distinguish 2 components of decision-making: decision uncertainty (DU) and emotion conflict (EC). This transdiagnostic sample was examined because AAC has particular relevance for both emotional and substance use disorders. Given their high comorbidity, it also provided the opportunity to examine possible dimensional and transdiagnostic effects, as well as assess differences that could be specific to some disorders and not others. Relative to healthy controls, both patient groups showed greater DU (associated with more inconsistent choice). Those with substance use disorders also showed reduced EC (associated with less avoidance of negative affective images/sounds when paired with various levels of reward), with the depression/anxiety group showing a similar pattern only in females (this difference in EC between the depression/anxiety and healthy control groups was also stronger when accounting for 1-year follow-up data[10]). While potentially important, the generalizability of these results was unclear, and a replication study with a new sample was warranted. In this report, we replicate our prior study in a new sample of patients meeting criteria for the same categories of mental health disorders, using the same computational model and the same AAC task. We show which findings replicate and which should be afforded less confidence. We also investigated whether results differed between specific substance use disorders and affective disorders, or whether a similar pattern held across diagnoses.

Methods

Participants

Participants for this preregistered analysis (preregistration at https://osf.io/7c96t) were identified from the confirmatory subsample (n = 550) of the Tulsa 1000 (T1000) study[11] — a naturalistic longitudinal study recruiting both healthy individuals and individuals expressing elevated psychiatric symptoms based on the dimensional National Institute of Mental Health Research Domain Criteria framework. The T1000 study included a community-based sample of 1050 individuals recruited through radio, electronic media, treatment centre referrals and word of mouth. Participants were 18–55 years of age, screened on the basis of dimensional psychopathology scores: Patient Health Questionnaire (PHQ[12]) ≥ 10, Overall Anxiety Severity and Impairment Scale (OASIS[13]) ≥ 8, and/or Drug Abuse Screening Test (DAST-1014) score ≥ 3. Healthy controls did not show elevated symptoms or psychiatric diagnoses. Participants were excluded if they tested positive for drugs of abuse; met criteria for psychotic, bipolar, or obsessive–compulsive disorders; or reported history of moderate to severe traumatic brain injury, neurologic disorders, or severe or unstable medical conditions, active suicidal intent or plan, or change in medication dose within 6 weeks. Full inclusion/exclusion criteria have been described previously.[11] The study was approved by the Western Institutional Review Board. All participants provided written informed consent before completion of the study protocol, in accordance with the Declaration of Helsinki, and were compensated for participation (ClinicalTrials.gov identifier: #NCT02450240). Previous studies have been published from the larger T1000 data set.[15–26] Our prior publications on the AAC task used data collected from the first 500 participants of the T1000 study, whereas the present study focuses on the confirmatory data set from the latter 550 participants.

As done in our previous study, after initial data quality control, participants were divided into 3 transdiagnostic groups: major depressive disorder (MDD) and/or comorbid anxiety disorders (social anxiety disorder [SAD], generalized anxiety disorder [GAD], panic disorder and/or posttraumatic stress disorder [PTSD]); substance use disorders (recreational drugs excluding alcohol and nicotine, with or without comorbid depression and anxiety disorders); and healthy controls with no mental health diagnoses. Figure 1 provides detailed information about the proportions and comorbidities across specific diagnoses and compares these to the previous sample. Diagnosis was based on DSM-IV or DSM-5 criteria using the Mini International Neuropsychiatric Inventory (MINI).[27] These categories were developed before the present analyses and have been discussed in previous papers.[15] While the T1000 study also included individuals with eating disorders, they were excluded here owing to small sample sizes. Depression/anxiety disorders were categorized together for our analyses owing to the high rates of overlap in these diagnoses and to there being very small sample sizes for anxiety disorders if separated (Figure 1).

Data collection procedure

T1000 participants underwent an intensive assessment for demographic, clinical and psychiatric features, with a focus on negative and positive affect, arousal and cognitive functioning. The complete list of assessments and references supporting their validity and reliability have been reported previously.[11] For this study, as in our prior paper, we included scores on the Wide Range Achievement Test reading subtest (WRAT[28]), which approximates baseline intellectual functioning.

Approach–avoidance conflict task

The AAC task[29,30] is described more extensively in our prior article[9] and in Figure 2 and Appendix 1 (available at www.jpn.ca/lookup/doi/10.1503/jpn.220226/tab-related-content). The task has 5 trial types. In each trial type, participants can choose to approach or avoid 2 outcomes, corresponding to combinations of either negative or positive affective stimuli and either 0, 2, 4 or 6 reward points. The trial types were as follows:

		Substance use disorders										Affective disorders							
		Alc.	Can.	Stim.	Op.	Sed.	Hal.	3+ SUDs	Single SUD	**Total (159)**		GAD	MDD	SAD	Panic	PTSD	3+ affect	Single affect	**Total (159)**
Substance use disorders	Alcohol		32 (20%)	41 (26%)	22 (14%)	20 (13%)	5 (3%)	37 (23%)	1 (1%)	**55 (35%)**	-	10 (6%)	30 (19%)	6 (4%)	8 (5%)	7 (4%)	7 (4%)	19 (12%)	**36 (23%)**
	Cannabis	30 (17%)		62 (39%)	33 (21%)	29 (18%)	11 (7%)	57 (36%)	7 (4%)	**84 (53%)**	-	12 (8%)	44 (28%)	12 (8%)	15 (9%)	17 (11%)	15 (9%)	32 (20%)	**52 (33%)**
	Stimulant	58 (33%)	67 (38%)		43 (27%)	29 (18%)	7 (4%)	54 (34%)	26 (16%)	**121 (76%)**	-	17 (11%)	53 (33%)	11 (7%)	10 (6%)	21 (13%)	11 (7%)	54 (34%)	**67 (42%)**
	Opioid	18 (10%)	24 (14%)	47 (27%)		30 (19%)	7 (4%)	42 (26%)	4 (3%)	**64 (40%)**	-	13 (8%)	37 (23%)	11 (7%)	12 (8%)	12 (8%)	12 (8%)	19 (12%)	**45 (28%)**
	Sedative	17 (10%)	19 (11%)	35 (20%)	25 (14%)		5 (3%)	39 (25%)	1 (1%)	**43 (27%)**	-	8 (5%)	20 (13%)	5 (3%)	8 (5%)	9 (5%)	8 (5%)	18 (11%)	**25 (16%)**
	Hallucinogen	1 (1%)	2 (1%)	3 (2%)	1 (1%)	1 (1%)		10 (6%)	0 (0%)	**11 (7%)**	-	2 (1%)	5 (3%)	2 (1%)	2 (1%)	5 (3%)	4 (3%)	4 (3%)	**7 (4%)**
	3+ SUDS	44 (25%)	47 (27%)	63 (36%)	36 (21%)	31 (18%)	3 (2%)		-	**67 (42%)**	-	12 (8%)	35 (22%)	9 (6%)	14 (9%)	14 (9%)	12 (8%)	22 (14%)	**45 (28%)**
	Single SUD	1 (1%)	2 (1%)	36 (21%)	4 (2%)	0 (0%)	0 (0%)	-		**41 (26%)**	-	4 (3%)	18 (31%)	6 (4%)	3 (2%)	4 (3%)	3 (2%)	14 (9%)	**23 (14%)**
	TOTAL (175)	**63 (36%)**	**74 (42%)**	**157 (90%)**	**58 (33%)**	**41 (23%)**	**3 (2%)**	**66 (38%)**	**44 (25%)**		**Total →**	**26 (16%)**	**80 (50%)**	**20 (13%)**	**20 (13%)**	**25 (16%)**	**21 (13%)**	**63 (40%)**	**96 (60%)**
		-	-	-	-	-	-	-	-	**Total ↓**		**Depression/anxiety group**							**Total (260)**
Affective disorders	GAD	11 (6%)	20 (11%)	33 (19%)	11 (6%)	12 (7%)	1 (1%)	15 (9%)	6 (3%)	**36 (21%)**	-		95 (37%)	24 (9%)	28 (11%)	14 (5%)	49 (19%)	9 (3%)	**110 (42%)**
	MDD	42 (24%)	45 (26%)	98 (56%)	43 (25%)	27 (15%)	2 (1%)	43 (25%)	27 (15%)	**113 (65%)**	-	94 (45%)		44 (17%)	47 (18%)	49 (19%)	59 (23%)	71 (27%)	**235 (90%)**
	Social anxiety	15 (9%)	19 (11%)	28 (16%)	10 (6%)	7 (4%)	0 (0%)	15 (9%)	4 (2%)	**33 (19%)**	-	37 (18%)	56 (27%)		9 (3%)	10 (4%)	30 (12%)	2 (1%)	**48 (18%)**
	Panic	3 (2%)	3 (2%)	10 (6%)	3 (2%)	3 (2%)	1 (1%)	4 (2%)	5 (3%)	**11 (6%)**	-	22 (13%)	26 (13%)	10 (5%)		52 (20%)	33 (13%)	2 (1%)	**52 (20%)**
	PTSD	9 (5%)	6 (3%)	15 (9%)	5 (3%)	7 (4%)	0 (0%)	7 (4%)	5 (3%)	**18 (10%)**	-	13 (6%)	28 (13%)	8 (4%)	2 (1%)		21 (8%)	2 (1%)	**52 (20%)**
	3+ affect	9 (5%)	12 (7%)	23 (13%)	7 (4%)	9 (5%)	1 (1%)	11 (6%)	4 (2%)	**25 (14%)**	-	54 (26%)	58 (28%)	38 (18%)	25 (12%)	17 (8%)		-	**60 (23%)**
	Single affect	16 (9%)	20 (11%)	48 (27%)	12 (7%)	12 (7%)	1 (1%)	16 (9%)	17 (10%)	**49 (28%)**	-	5 (2%)	57 (27%)	2 (1%)	0 (0%)	0 (0%)	-		**86 (33%)**
	TOTAL (175)	**47 (27%)**	**54 (31%)**	**109 (62%)**	**46 (26%)**	**29 (17%)**	**2 (1%)**	**50 (29%)**	**30 (17%)**	**126 (79%)**	**Total (208)**	**105 (50%)**	**191 (92%)**	**63 (30%)**	**29 (14%)**	**28 (13%)**	**60 (29%)**	**64 (31%)**	**Total (958)**

Figure 1: Lifetime DSM-IV/DSM-5 psychiatric diagnosis composition within exploratory (above diagonal) and confirmatory (below diagonal) samples. Four individuals with depression/anxiety disorders in the exploratory sample and 4 in the confirmatory sample were included only in the total counts because they had unspecified depressive disorders (3 exploratory, 2 confirmatory) and/or showed bipolar (2 confirmatory) or psychotic symptoms (1 exploratory). Alc. = alcohol use disorders; Can. = cannabis use disorders; DU = decision uncertainty; EC = emotion conflict; GAD = generalized anxiety disorder; Hal. = hallucinogen use disorders; MDD = major depressive disorder; Op. = opioid use disorders; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder; Sed. = sedative use disorders; Stim. = stimulant use disorders; SUD = substance use disorder.

- "Avoid-threat" (AV), in which 0 points were offered for both possible stimulus outcomes and, thus, the only explicit motivation was to avoid the negative affective stimulus.
- "Approach-reward" (APP), in which 2 versus 0 points were offered, each with positive affective stimuli. For this condition, the only explicit motivation was to approach the rewarded outcome.
- Three levels of "Conflict" in which the negative affective stimulus was presented in addition to winning either 2 (CONF2), 4 (CONF4) or 6 (CONF6) points, while 0 points were offered for the other possible outcome, in which a positive affective stimulus would be presented.

As in previous administrations of the task,[29,31] points did not correspond to monetary reward. That is, participants did not receive additional monetary compensation based on the number of points they earned. Points were therefore assumed to be rewarding in and of themselves within the context of the task. Notably, previous research has shown that paradigms involving either non-monetary or monetary reward elicit similar neural activation patterns in reward-sensitive brain regions,[32,33] which could suggest similar motivational influences. Previous studies using this task with and without monetary compensation have also found similar patterns of behaviour.[29,34]

Descriptive behavioural variables consisted of average chosen runway position, within-subject standard deviation in chosen runway position, and response times (RTs; i.e., time to initial button press) during each trial.

After completing all trials, participants filled out a short Likert scale questionnaire about their experiences/behaviours during the task.

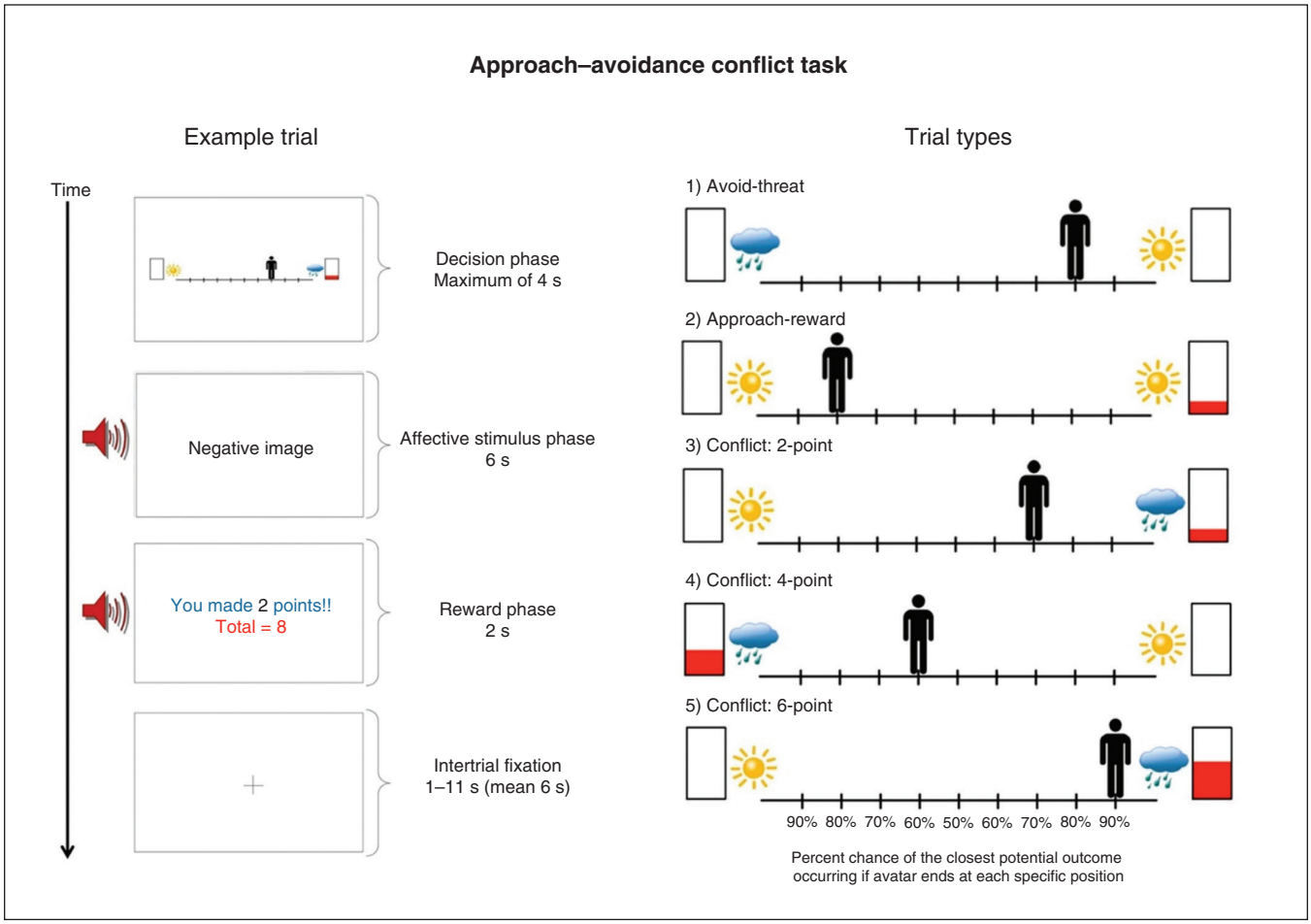

Figure 2: Diagram representing the approach–avoidance (AAC) task. On each trial, participants choose to move an avatar to 1 of 9 positions on a runway. Pictures are shown on each side of the runway, indicating the types of stimuli that could be presented at the end of the trial. A sun or cloud represented potential positive or negative affective stimuli, respectively (each being an image–sound combination), while the height of the red fill in a rectangle signified the number of points that would be received in conjunction. Participants were told the ending position of the avatar determined the probability of each of these outcomes occurring (in increments of 10%, from 90% to 10% with each step away from the associated stimulus indicator images). (Left) Example trial, in which the negative stimulus and 2 points were presented based on the probabilities associated with the chosen runway position. (Right) The 5 trial types and associated probabilities of each outcome at each runway position. The task consisted of a total of 60 trials, with 12 of each of the 5 trial types. After task completion, a screen appeared displaying total points received and an award ribbon. Adapted from our previous paper.[9]

Computational modelling

The generative model of the AAC task and active inference scheme used for computational analyses has been described in detail in our previous articles;[9,35] for a detailed tutorial covering the general structure and mathematics of this class of models, see Smith and colleagues.[36] A description of each element of the generative model is provided in Table 1. The model afforded estimation of parameters reflecting the subjective aversiveness of the negative image–sound combinations relative to the value of the points ("emotion conflict"; EC) and the level of uncertainty in decision-making, where greater uncertainty promotes less consistent choices within each trial type ("decision uncertainty"; DU). Considerations of parameter recoverability and alternative models have been described previously.[9]

Estimates of the DU and EC parameters were optimized to match the choice behaviour of each participant, where the resulting parameter values could then be used as individual difference measures capturing regularities in their decision processes. Technically, this involved searching over combinations of DU and EC values to maximize the likelihood of each participant's choices across trials, which was accomplished using a standard variational Bayesian approach called Variational Laplace.[37]

Statistical analysis

Our main analyses focused on replicating those used in our previous study.[9] These analyses were conducted using the R statistical package (2018; www.R-project.org/). We first calculated a model accuracy score reflecting the average percentage

Table 1: Markov decision process model of the approach–avoidance conflict task

Model element	General Definition	Model-specific specification
o_τ	Observable outcomes at time τ	Outcome modalities correspond to vectors encoding: 1. Observed position on the runway (10 possible observations, including a "starting" position and the 9 final positions on the runway that one could choose 2. Cues indicating trial type (5 possible observations, corresponding to the 5 trial types) 3. Stimuli observed at the end of each trial. This included 7 possible observations corresponding to a "starting" observation, the unpleasant stimulus with 0 points, the pleasant stimulus with 0 or 2 points, and the unpleasant stimulus with 2, 4 or 6 points.
s_τ	Hidden states at time	Hidden state factors correspond to vectors encoding: 1. Possible positions on the runway (10 possible states with an identity mapping to the observations in outcome modality #1) 2. Possible trial types (5 possible states with an identity mapping to the observations in outcome modality #2)
$p(o_\tau \mid s_\tau)$	A set of matrices encoding beliefs about the association between hidden states and observable outcomes (i.e., the likelihood that specific outcomes will be observed given specific hidden states)	Encodes beliefs about the association between position on the runway, the trial type and the probability of observing each outcome, conditional on beliefs about the trial type. The model is constructed such that cues provide complete certainty about the trial type and runway position (i.e., only the outcomes under different combinations of runway positions and trial types are probabilistic). In these matrices, columns (states) from left to right indicate the starting state followed by possible final position states 1 through 9. Rows from top to bottom indicate the possible observations in modality #3 above (outcome stimuli). This includes the starting observation ("no stimulus"), followed by observations of: unpleasant stimuli, pleasant stimuli, pleasant stimuli + 2 points, unpleasant stimuli + 2 points, unpleasant stimuli + 4 points, and unpleasant stimuli + 6 points. For an explicit depiction of these matrices, see Appendix 1, available at www.jpn.ca/lookup/doi/10.1503/jpn.220226/tab-related-content
$p(s_{\tau+1} \mid s_\tau, \pi)$	A set of matrices encoding beliefs about how hidden states will evolve over time (transition probabilities) under each possible action sequence or policy (π)	Encodes beliefs about the way participants could choose to move the avatar, as well as the belief that the trial type will not change within a trial. These simply indicated that: $p(s_{\tau=2}^{\text{chosen position}} \mid s_{\tau=1}^{\text{start}}, s_{\tau=1}^{\text{trial type}}, \pi^{\text{chosen position}}) = 1$
$p(o_\tau \mid C)$	A matrix encoding the degree to which some observed outcomes are preferred over others at each time point τ (where a higher probability value corresponds to being more preferred). Preferences at each time point are encoded in a vector C and then normalized with a softmax operator (σ)	Encodes stronger positive preferences for receiving higher amounts of points, and negative preferences for the unpleasant stimuli (both relative to an anchor value of 0 for the "safe" positive stimulus). The EC parameter encodes the estimated value of participants' preferences against observing the unpleasant stimuli as follows (with each element corresponding to the respective rows within $p(o_\tau \mid s_\tau)$): $p(o_\tau \mid C) = \sigma([0\ -EC\ 0\ 2\ -EC + 2\ -EC + 4\ -EC + 6]^T)$
$p(s_1)$	A set of vectors encoding beliefs about (a probability distribution over) initial hidden states for each state factor	The simulated participant always begins in the initial starting state with $p = 1$, and each trial type is equally likely (before observing the trial type cues).
$G(\pi)$	This is the EFE of a policy (π), which is used to evaluate which policies are better than others: $G(\pi) =$ $-E_{q(o,s\mid\pi)}[\ln q(s_\tau \mid o_\tau, \pi) - \ln q(s_\tau \mid \pi)]$ $-E_{q(o\mid\pi)}[p(o_\tau \mid C)]$ The first term on the right of the equation motivates decisions that will seek out information to reduce uncertainty about states. The second term motivates decisions that are expected to maximize the probability of preferred observations (encoded in C). Note that q denotes an approximate posterior distribution (reflecting a best guess about the associated probabilities).	In this case, the value of the EC parameter within $p(o_\tau \mid C)$ determines the magnitude of the negative preference for observing the unpleasant stimuli, which motivates the selection of policies that will favour only observing points that have greater values than EC. Note that, as there is no uncertainty about current trial type or runway position in this task, the information-seeking term within $G(\pi)$ does not play a crucial role in this context. An alternative decomposition of the expected free energy — into terms often referred to as "risk" and "ambiguity" — also implies that, in the absence of any ambiguity (as in the present task), participants will aim to minimize the divergence between predicted and preferred outcomes (i.e., risk).
β	The prior on EFE precision (β) is the "rate" parameter of a γ distribution, the expected value of which is γ. Assuming a "shape" parameter value of 1, $\gamma = 1 \div \beta$. This term is used as a scalar that modulates the precision of the EFE distribution over policies. A policy with lower EFE entails a higher probability of generating preferred outcomes under the model (see entry for $G(\pi)$ above).	When β is high (reflecting low confidence about the best decision), policy selection becomes less deterministic. Higher β values therefore encode participants' decision uncertainty during the task. This β value was estimated for each participant. In the main text, we refer to this as the DU parameter.
$q(\pi)$	An approximate posterior distribution over action policies (π) encoding the probability of selecting a particular policy, based on its EFE: $q(\pi) = \sigma(-\gamma G)^*$ The γ term is described in the previous entry.	Allowable policies included the decision to transition from the starting state to each of the 9 possible positions on the runway. Policies with lower EFE have a higher probability of being selected.

DU = decision uncertainty; EC = emotion conflict; EFE = expected free energy.
*Here, σ indicates a softmax operator that converts a vector of values into a proper probability distribution (with non-negative values that sum to 1).

of trials during which the action with the highest probability in the computational model matched the true action chosen by participants (i.e., under the parameter values estimated for each participant). We then examined correlations between model parameters and RTs, with the expectation that computational measures of greater EC and DU would both be associated with slower RTs. We then conducted further correlation analyses to examine whether each parameter could predict

subsequent self-reports on post-task Likert scale questions (i.e., identical to those used in our previous study). We expected EC would be associated with self-reported avoidance motivation and anxiety, and that DU would be positively associated with self-reported difficulty making decisions and self-reported avoidance motivation.

We conducted type 2 analyses of variance (ANOVA) to identify possible group differences in each parameter. Type 2 analyses of covariance (ANCOVA) were then completed to confirm that these differences remained significant after accounting for individual differences in age and sex, and the interaction between group and each of these factors. To interpret significant results, post hoc contrasts were carried out using estimated marginal means with proportional weighting. JZS Bayes factor analyses (with default prior scales; "Bayesfactor" package[38–40]) were also carried out to assess which combination of possible predictors/covariates best accounted for variance in each model parameter. As in our previous report, we also planned to include main effects and interactions with WRAT reading scores in these ANCOVAs to assess whether group differences in task behaviour could be accounted for by differences in baseline intellectual functioning. However, owing to issues that arose in data collection, 85 participants did not have WRAT reading scores (12 healthy controls, 22 depression/anxiety, 51 substance use disorder). Thus, identical analyses were instead run with and without WRAT scores as a covariate to avoid removing these 85 participants from all primary analyses. We expected to observe greater DU parameter values in the depression/anxiety and substance use disorder groups than in healthy controls. We also expected greater EC in people with substance use disorders than in healthy controls.

As complementary secondary analyses, we also conducted identical ANOVAs/ANCOVAs to those described above with standard descriptive task variables as the dependent variables, including mean and within-subject standard deviation in chosen runway positions, and RTs during the different task trial types. Based on our prior results,[9,10] we expected to observe slower RTs in the clinical groups than in healthy controls, less approach behaviour (in mean runway position) in healthy controls than in the clinical groups, and greater within-subject choice variance in the clinical groups than in healthy controls. As all analyses aimed to replicate prior significant results, we did not correct for multiple comparisons.

In our previous study, exploratory analyses indicated that the group differences in EC were present in females and not males when examined separately. In contrast, the group differences in DU were present in males but not females when examined separately. Analyses conducted to test whether these results would replicate are described in Appendix 1.

Group differences in WRAT reading scores (lower scores in the substance use disorder group than in the other groups) were anticipated based on the representative demographics within these clinical populations (e.g., see[41–48]). As in our previous study, we planned to use the fullmatch function within the optmatch[1] R package (https://www.rdocumentation.org/packages/optmatch/versions/0.9-10/topics/fullmatch) to propensity-match groups based on WRAT reading scores and then perform the same analyses described above with the propensity-matched subsamples. In our prior study, we also propensity-matched on age (propensity-matching on sex was also attempted but was unsuccessful, and so sex was included as a covariate in those analyses). The present sample did not have significant differences in age, which precluded the need for matching on this variable. Unfortunately, the composition of the present sample led to an inability to successfully propensity-match on WRAT reading scores when the matching algorithm was applied (i.e., significant group differences could not be removed owing to insufficient overlap). This reflected the significantly lower WRAT reading scores in the current substance use disorder sample compared with that of our previous study (Appendix 1). As such, we report only analyses on the full sample. We include results both with and without age, sex and WRAT reading score as covariates.

Disorder-specific analyses in combined samples

After completing all preregistered replication analyses, we examined potential differences between individuals with specific disorders by combining the exploratory and confirmatory samples (as sample sizes in the exploratory sample alone did not permit this in our prior study). Using logistic regressions, we first examined whether model parameters could predict the presence of specific substance use or affective disorders relative to healthy controls. These regression models included both parameters (and their interactions with age and sex) as predictors of diagnostic status (i.e., coding healthy controls = 0 and those with the specific disorder in question = 1, removing all other participants). When possible, we also examined those with no comorbid disorders; however, rates of comorbidity were too high to do this in most cases. To further investigate potential effects of specific diagnoses, we then performed analogous logistic regressions to evaluate whether model parameters could predict the presence of a given disorder relative to all other disorders (i.e., removing healthy controls and coding those with v. without the specific disorder in question equal to 1 v. 0, respectively). Each of the logistic regressions above were performed separately for the depression/anxiety group and the substance use disorders group. We also used *t* tests to evaluate whether parameter values might differ in those with current compared with remitted MDD or in those with MDD with and without comorbid anxiety disorders.

Results

The sample in the present study included 480 participants: 97 healthy controls, 175 individuals with substance use disorders and 208 individuals with depression and/or anxiety disorders. Descriptive statistics for demographic and clinical measures are shown in Table 2. Mean ± standard deviation (SD) values for each of the parameters were as follows: DU 4.51 ± 5.06 and EC 2.62 ± 2.91. By group, these values were as follows: DU 3.96 ± 4.65 and EC 3.53 ± 3.57 in healthy controls, DU 4.14 ± 4.57 and EC 2.97 ± 3.06 in the depression/anxiety group, and DU 5.26 ± 5.73 and EC 1.70 ± 1.95 in the substance

use disorder grroup. For further analyses testing for potential differences in demographic/clinical variables between the previous and current samples and further information about the association between model parameters and demographic/clinical variables, see Appendix 1. The only demographic and clinical differences found between samples (all of small effect size) were that the previous depression/anxiety sample was older and had higher DAST scores than the current depression/anxiety sample and the previous substance use disorder sample had higher WRAT reading scores than the current substance use disorder sample.

The EC and DU parameters were correlated at $r = 0.24$, $p < 0.001$. As in our prior study, because the parameters were not normally distributed, they were log-transformed for all subsequent analyses using the R package optLog (https://github.com/kforthman/optLog) to find the optimal log-transform that minimizes skew. This resulted in the following log-transformed values: DU 0.91 ± 0.97 and EC 1.02 ± 0.79 in healthy controls, DU 0.95 ± 1.02 and EC 0.86 ± 0.79 in the depression/anxiety groups, and DU 1.19 ± 1.01 and EC 0.44 ± 0.68 in the substance use disorder group.

Face validity: task-related self-report and behaviour

Averaging across participants, the model was accurate at predicting behaviour in 75% (standard error 1.1%) of trials (chance accuracy 1/9 = 11%). Table 3 shows significant correlations between model parameters and each of 8 items (Q1–Q8) on the post-AAC task questionnaire. Notably, EC correlated most strongly with self-reported motivations to move toward reward points (Q4; $r = –0.73$, $p < 0.001$) and motivations to move away from negative images/sounds (Q5; $r = 0.72$, $p < 0.001$). As observed in our previous study, higher EC also corresponded to higher self-reported anxiety during the task (Q2; $r = 0.35$, $p < 0.001$). Also as observed previously, DU correlated most strongly with self-reported difficulty making decisions on the task (Q3; $r = 0.41$, $p < 0.001$) and motivations to move toward reward points (Q4; $r = –0.46$, $p < 0.001$). Individuals with longer RTs across all trials also showed higher EC ($r = 0.22$, $p < 0.001$) and DU values ($r = 0.57$, $p < 0.001$). Analyses of RTs within specific trial types showed similar results (EC: $0.22 \leq r \leq 0.31$; DU: $0.30 \leq r \leq 0.55$; Appendix 1, Figure S1), with the exception of the AV condition, where

Table 2: Demographic and clinical characteristics of the study sample

Characteristic	Group, mean ± SD*			*p* value†
	Healthy controls, *n* = 97	Depression/anxiety disorders, *n* = 208	Substance use disorders, *n* = 175	
Age, yr	32.09 ± 11.10	33.74 ± 10.17	33.76 ± 8.42	0.33
Sex (male), no. (%)	38 (39.17)	51 (24.5)	68 (38.9)	0.004
PHQ score	1.23 ± 1.82	12.53 ± 5.00	6.59 ± 5.76	< 0.001
OASIS score	1.10 ± 1.62	9.65 ± 3.58	5.77 ± 4.46	< 0.001
DAST-10 score	0.19 ± 0.49	0.41 ± 0.95	7.46 ± 2.23	< 0.001
WRAT reading score	62.81 ± 5.31	62.75 ± 5.06	56.79 ± 6.78	< 0.001

DAST = Drug Abuse Screening Test; OASIS = Overall Anxiety Severity and Impairment Scale; PHQ = Patient Health Questionnaire; WRAT = Wide Range Achievement Test.
*Unless indicated otherwise.
†*p* values are based on ANOVAs testing for significant differences between the 3 groups.

Table 3: Post-task self-report questionnaire items and Pearson correlations with computational model parameters (*n* = 480)

Post-task self-report questions*	Mean ± SD	EC parameter	DU parameter
Q1. I found the positive pictures enjoyable:	5.02 ± 1.56	0.03	–0.01
Q2. The negative pictures made me feel anxious or uncomfortable:	4.00 ± 1.97	0.34†	0.14†
Q3. I often found it difficult to decide which outcome I wanted:	2.32 ± 1.71	0.08	0.41†
Q4. I always tried to move all the way toward the outcome with the largest reward points:	4.87 ± 2.35	–0.73†	–0.46†
Q5. I always tried to move all the way away from the outcome with the negative pictures/sounds:	2.86 ± 2.15	0.72†	0.35†
Q6. When a negative picture and sound were displayed, I kept my eyes open and looked at the picture:	5.43 ± 1.89	–0.43†	–0.24†
Q7. When a negative picture and sound were displayed, I tried to think about something unrelated to the picture to distract myself:	2.84 ± 1.90	0.29†	0.04
Q8. When a negative picture and sound were displayed, I tried other strategies to manage emotions triggered by the pictures	3.04 ± 1.91	0.35†	0.11‡

DU = decision uncertainty; EC = emotional conflict; SD = standard deviation.
*Likert scale, where 1 = not at all and 7 = very much.
†$p < 0.001$.
‡$p < 0.05$.

RTs were faster in those with greater EC ($r = –0.21$, $p < 0.001$), as expected (i.e., more confident avoidance would be expected in the absence of any points on offer). Several of these correlations are illustrated in Figure 3.

Clinical validity: diagnostic effects

With respect to DU, an initial ANOVA revealed a significant main effect of clinical group ($F_{2,477} = 3.52$, $p = 0.026$; Figure 4). Post hoc t tests indicated that this effect was due to higher DU in the substance use disorder group than in healthy controls ($t_{270} = 2.20$, $p = 0.029$, $d = 0.28$) and the depression/anxiety group ($t_{381} = 2.31$, $p = 0.022$, $d = 0.24$), but a nonsignificant difference between healthy controls and the depression/anxiety group ($t_{303} = 0.29$, $p = 0.771$, $d = 0.04$). As shown in Table 4, this effect remained significant in an ANCOVA including possible main effects and interactions with age and sex. Decision uncertainty was also positively associated with age, and there was an interaction with group indicating a stronger relationship between age and DU in the substance use disorder group than in healthy controls. While there was not a sex × group interaction, preregistered supplementary analyses testing effects in each sex separately suggested group effects were more driven by males, a result qualitatively similar to that in the previous sample (Appendix 1, Figure S4). Bayes factor analyses testing evidence for models that did or did not contain main effects of age and sex, and their respective interactions with group, found the most evidence for a model that included only an effect of age (BF > 100 relative to an intercept-only model); the second-best model added an effect of group (BF > 100 relative to an intercept-only model; BF = 0.56 relative to the winning model). When including only participants with WRAT reading scores and adding possible main effects and interactions with WRAT reading scores into the ANCOVA model above, the effect of group was no longer significant (Appendix 1).

With respect to EC, an initial ANOVA revealed a significant main effect of clinical group ($F_{2,477} = 23.83$, $p < 0.001$; Figure 4). Post hoc t tests indicated that this effect was due to lower EC in the substance use disorder group than in healthy controls ($t_{270} = 6.46$, $p < 0.001$, $d = 0.82$) and the depression/anxiety group ($t_{381} = 5.57$, $p < 0.001$, $d = 0.57$), but a nonsignificant difference between healthy controls and the depression/anxiety group ($t_{303} = 1.67$, $p = 0.095$, $d = 0.21$). As shown in Table 4, this effect remained significant when accounting for possible effects of age and sex, and their interactions with group. When accounting for the other predictors in this model, post hoc contrasts also indicated that the difference between healthy controls and the depression/anxiety group became significant (i.e., greater EC in healthy controls; $t_{471} = 2.33$, $p = 0.020$, $d = 0.29$). However,

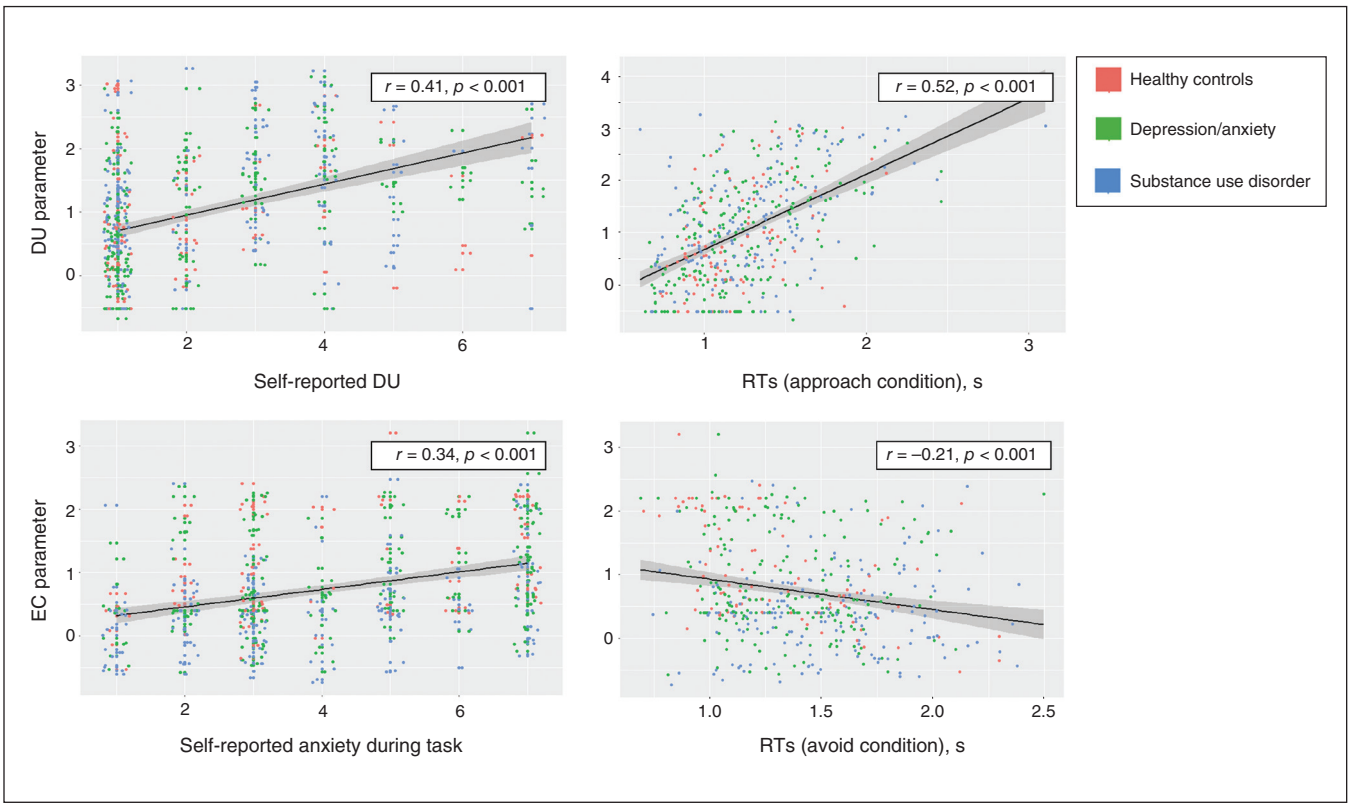

Figure 3: Scatterplots showing associations between model parameters and (left panels) self-reported task experience (Q2 and Q3 in Table 3) and (right panels) response times (RTs) in seconds in relevant task conditions. The substance use disorder group showed significantly different values than the other groups with respect to both model parameters and both RT measures. The depression/anxiety group also differed from healthy controls on emotion conflict (EC). Note that EC and decision uncertainty (DU) are shown in log-space.

there was a notable interaction between sex and group, indicating that all 3 groups differed significantly among females (healthy controls > depression/anxiety > substance use disorders), while no group differences were present in males (effect sizes for post hoc contrasts in females: healthy controls > depression/anxiety, $d = 0.42$; healthy controls > substance use disorders, $d = 1.15$; Table 4). Figure 5 shows a direct comparison between the previous and current samples (Appendix 1, Figure S4 shows an analogous plot for DU). Bayes factor analyses testing evidence for models that did or did not contain main effects of age and sex, and their respective interactions with group, found the most evidence for a model that included only the effect of group and the sex × group interaction (BF > 100 relative to an intercept-only model). In subsequent analyses including only participants with WRAT reading scores and adding possible main effects and interactions with WRAT reading scores into the ANCOVA model above, the effect of group remained significant ($F_{2,383} = 19.17$, $p < 0.001$), as did the sex × group interaction ($F_{2, 383} = 5.11$, $p = 0.006$). There was also a group × WRAT interaction ($F_{2, 383} = 6.60$, $p = 0.002$), reflecting a stronger positive association between WRAT score and EC in the depression/anxiety group than in the substance use disorder group ($t_{383} = 3.63$, $p < 0.001$; Appendix 1).

Exploratory t tests comparing those with depression with and without comorbid anxiety found no significant differences in any study variable, with the exception of RTs in the APP condition ($t_{194} = -2.08$, $p = 0.04$, $d = 0.32$), indicating slower RTs in those without comorbid anxiety. Correlation analyses reported in Appendix 1 revealed some notable positive associations between DU and anxiety in the depression/anxiety group; however these findings should be treated with caution, as they were not found in our prior study.

Secondary analyses of descriptive measures

Descriptive statistics for all model-free measures, as well as their correlations with model parameters, are provided in Appendix 1, Tables S1–S4 and Figures S1–S3. Results of

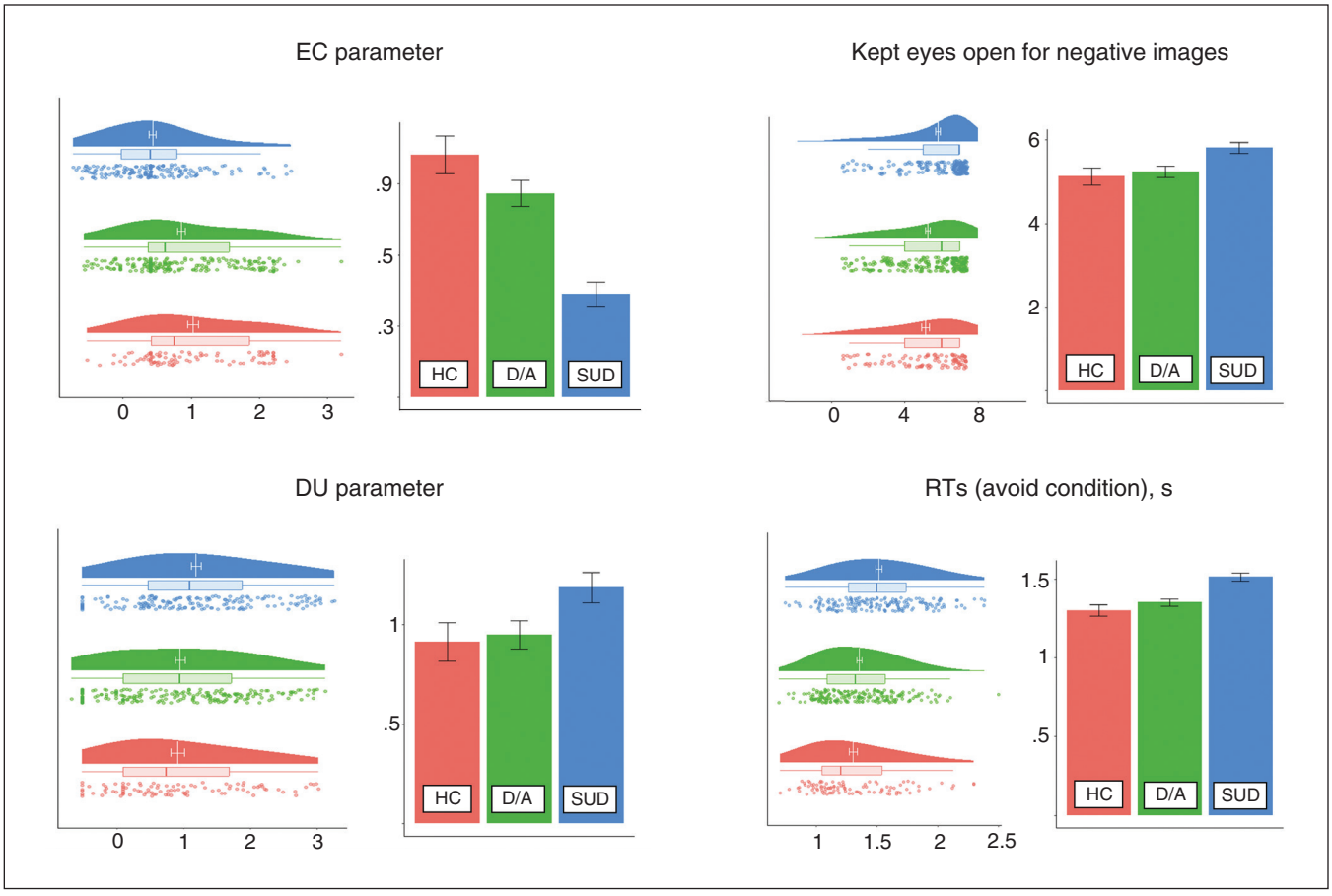

Figure 4: Raincloud plots (including densities, boxplots, means and standard errors [SEs], and individual data points) and bar plots (means and SEs) showing differences between healthy controls (HC) and clinical groups in 2 measures of avoidance (top row) and 2 measures of uncertainty (bottom row) in which values were significantly different in the substance use disorder (SUD) group compared with the other groups: The emotional conflict (EC) model parameter, reflecting expected aversiveness of negative stimuli relative to reward; a self-reported emotion regulation strategy (Q6 in Table 3; lower values indicate individuals closed their eyes more often to avoid the negative stimuli); the decision uncertainty (DU) model parameter, reflecting indeterminacy in choice; and response times (RTs) in seconds in the avoid condition. The depression/anxiety disorder group (D/A) also differed from healthy controls on EC. Note that EC and DU are shown in log-space.

Table 4: Results of ANCOVA models examining group differences in model parameters, when accounting for main effects and interactions with age and sex

Predictor*	Test, p value	B (95% CI), p value	Post hoc contrasts*
Emotion conflict			
Age	$F_{1, 471} = 5.02$, $p = 0.026$	0 (–0.01 to 0.02), $p = 0.569$	NS
Sex	$F_{1, 471} = 2.41$, $p = 0.121$	–0.23 (–0.39 to –0.08), $p = 0.002$	NS
Group	$F_{1, 471} = 24.83$, $p < 0.001$	D/A: –0.17 (–0.36 to 0.03), $p = 0.091$ SUD: –0.53 (–0.72 to –0.34), $p < 0.001$	HC–D/A: 0.22, $t_{471} = 2.33$, $p = 0.020$ HC–SUD: 0.64, $t_{471} = 6.75$, $p < 0.001$ D/A–SUD: 0.42, $t_{471} = 5.52$, $p < 0.001$
Age × group	$F_{2, 471} = 1.38$, $p = 0.253$	Age × D/A: 0 (–0.02 to 0.02), $p = 0.916$ Age × SUD: 0.01 (–0.01 to 0.03), $p = 0.153$	NS
Sex × group	$F_{2, 471} = 5.55$, $p = 0.004$	Sex × D/A: 0.14 (–0.05 to 0.33), $p = 0.144$ Sex × SUD: 0.32 (0.13 to 0.51), $p = 0.001$	Male HC–D/A: 0.02, $t_{471} = 0.14$, $p = 0.887$ HC–SUD: 0.21, $t_{471} = 1.40$, $p = 0.163$ D/A–SUD: 0.19, $t_{471} = 1.36$, $p = 0.174$ Female HC–D/A: 0.31, $t_{471} = 2.74$, $p = 0.007$ HC–SUD: 0.85, $t_{471} = 7.03$, $p < 0.001$ D/A–SUD: 0.54, $t_{471} = 5.77$, $p < 0.001$
Decision uncertainty			
Age	$F_{1, 471} = 32.56$, $p < 0.001$	0.01 (–0.01 to 0.03), $p = 0.27$	NS
Sex	$F_{1, 471} = 3.28$, $p = 0.071$	–0.1 (–0.3 to 0.09), $p = 0.301$	NS
Group	$F_{1, 471} = 3.69$, $p = 0.026$	D/A: –0.02 (–0.27 to 0.23), $p = 0.871$ SUD: 0.26 (0.01 to 0.51), $p = 0.042$	HC–D/A: 0.02, $t_{471} = 0.15$, $p = 0.884$ HC–SUD: –0.24, $t_{471} = –1.94$, $p = 0.053$ D/A–SUD: –0.26, $t_{471} = –2.57$, $p = 0.011$
Age × group	$F_{2, 471} = 3.71$, $p = 0.025$	Age × D/A: 0.02 (–0.01 to 0.04), $p = 0.155$ Age × SUD: 0.03 (0.01 to 0.06), $p = 0.007$	HC–D/A: –0.02, $t_{471} = –1.42$, $p = 0.155$ HC–SUD: –0.04, $t_{471} = –2.72$, $p = 0.007$ D/A–SUD: –0.02, $t_{471} = –1.66$, $p = 0.097$
Sex × group	$F_{2, 471} = 0.17$, $p = 0.847$	Sex × D/A: –0.01 (–0.26 to 0.24), $p = 0.941$ Sex × SUD: 0.05 (–0.2 to 0.3), $p = 0.688$	NS

ANCOVA = analysis of covariance; CI = confidence interval; D/A = depression/anxiety disorder group; HC = healthy control group; NS = nonsignificant; SUD = substance use disorder group.
*For interpretability, continuous predictors were centred, sum coding was used for sex (female = –1; male = 1), and treatment coding was used for group (with healthy controls as the reference group, coded as 0).

ANOVAs/ANCOVAs on descriptive measures are also described in Appendix 1, Tables S5–S8. These results largely replicated those in our previous paper and were consistent with the differences found in model parameter values, including group differences in average chosen runway position in each task condition except APP (greater avoidance in healthy controls than in 1 or both clinical groups); choice SDs in the AV and APP conditions (greater in the substance use disorder group than in the other groups); RTs in the AV condition and marginally in the APP condition (slower in the substance use disorder group and females in the depression/anxiety group than in healthy controls; Figure 4); and several self-reported task responses (greater self-reported avoidance and use of emotion regulation strategies in healthy controls than in the substance use disorder group; Figure 4).

Disorder-specific effects in combined cohorts

Descriptive statistics for model parameters in the combined exploratory and confirmatory sample, when grouped by specific disorder, are presented in Appendix 1, Table S9. Full results of logistic regression models, which either differentiated healthy controls from those with specific disorders or differentiated one disorder from others, are shown in Figure 6 and in Appendix 1, Tables S10–S13. In the substance use disorder group, both DU and EC could differentiate healthy controls from those with each specific substance use disorder (DU: Wald $z = 2.48$ to 4.54, $p < 0.001$ to 0.013; EC: Wald $z = –7.01$ to –2.43, $p < 0.001$ to 0.015), as well as those with most affective disorders (Figure 6, middle panels, and Appendix 1, Table S10). Both DU and EC could also differentiate healthy controls from stimulant users without comorbid disorders (Wald $z = 2.96$ to –4.56, all $p < 0.001$; Figure 6, bottom panels). Sample sizes were too small to assess other substance use disorders without comorbidities (Figure 1). Analogous logistic regressions were unable to differentiate specific substance use disorders from one another.

In the depression/anxiety group, EC could differentiate healthy controls from those with each specific affective disorder (Wald $z = –3.97$ to –1.99, $p < 0.001$ to 0.046), while DU could only differentiate healthy controls from those with MDD (Wald $z = 2.12$, $p = 0.034$; Figure 6, top panels). When restricting analyses to those without comorbidities, EC could differentiate healthy controls from those with MDD alone (Wald $z = –3.50$, $p < 0.001$), while DU could only differentiate individuals with MDD who also had comorbid anxiety (Wald $z = 1.96$, $p = 0.050$; Figure 6, bottom panels). However,

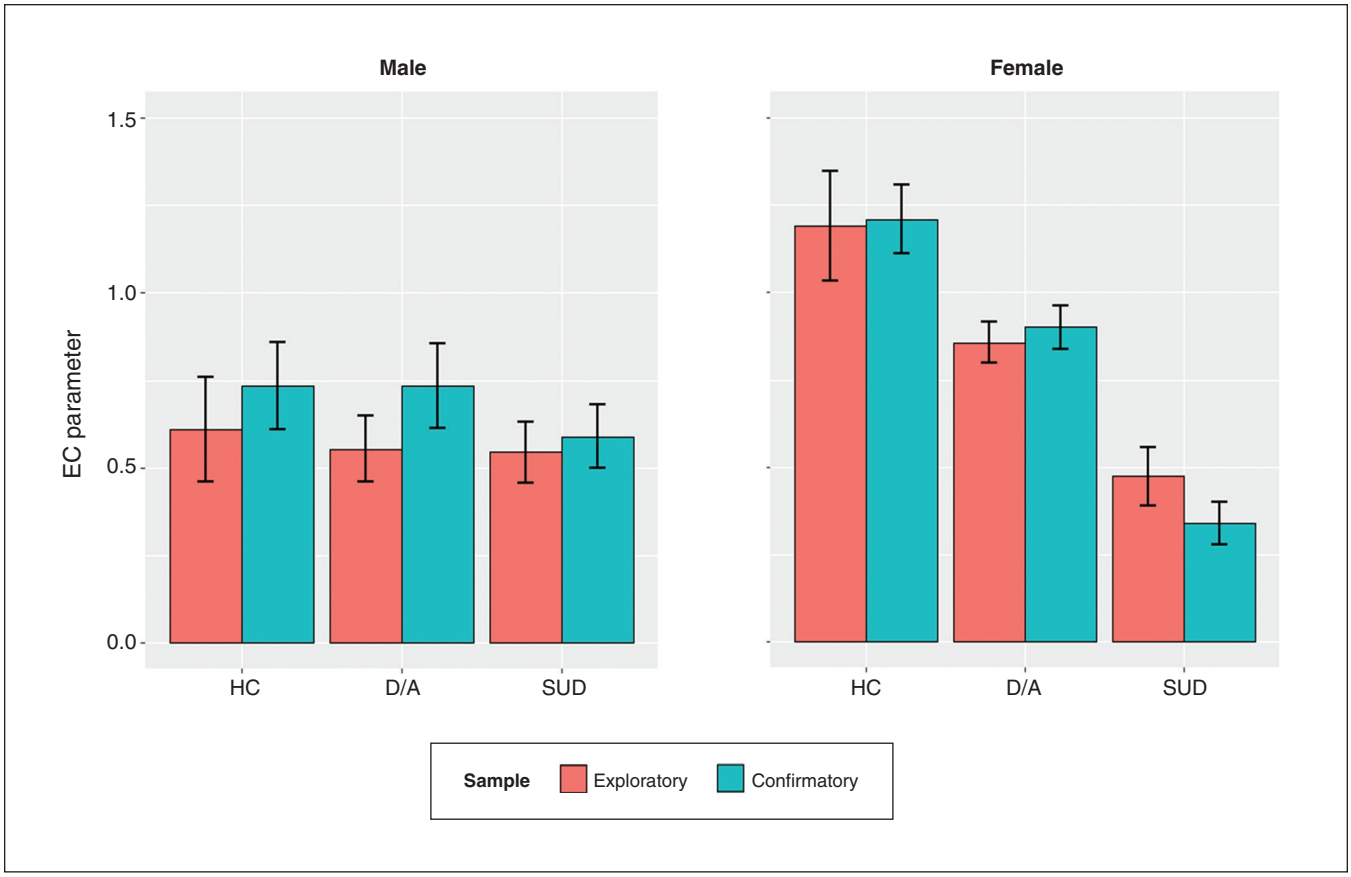

Figure 5: Comparison of results (means with standard errors) for the emotion conflict (EC) parameter in our previous study[9] and the current sample when separated by clinical group and sex. This illustrates the consistency of prior results with the interaction between group and sex found in the present study, indicating reduced avoidance (EC) in both clinical groups in females compared with healthy controls (HC). D/A = depression/anxiety disorder group; SUD = substance use disorder group.

the qualitative pattern was similar for MDD alone (and this group had a notably smaller sample size). In analogous logistic regressions removing healthy controls, DU was able to differentiate social anxiety disorder from other affective disorders (i.e., lower DU values than other disorders; Wald z = –3.11, p = 0.002; Figure 6, top right panel), while EC could not differentiate between affective disorders.

Notably, significant interactions were present between sex and EC, reflecting greater effects in females for MDD alone (i.e., without comorbidities), but not for other depression/anxiety subgroups (Appendix 1, Figure S5–S6). In contrast, these interactions were present for most specific substance use disorders, with the exception of sedative and hallucinogen use disorders (the sample size for hallucinogen users was especially small; Appendix 1, Table S10). Interactions with sex were not observed when removing healthy controls and attempting to differentiate between disorders (Appendix 1, Table S11).

No differences were found for either parameter when comparing current and remitted MDD (n = 286 and 38, respectively; DU: t_{322} = 0.41, p = 0.68; EC: t_{322} = –0.83, p = 0.405), or when comparing MDD with and without comorbid anxiety (n = 298 and 128, respectively; DU: t_{424} = –0.76, p = 0.45; EC: t_{424} = –0.33, p = 0.745).

Discussion

In this study, we found confirmatory evidence for both greater DU and reduced EC in people with substance use disorders relative to healthy controls (with small to moderate and large effect sizes, respectively), as well as consistent patterns of greater approach behaviour during conflict, and less avoidance, greater choice variability, and slower RTs in the absence of conflict. Females, but not males, in the depression/anxiety group showed a similar pattern of reduced avoidance (i.e., lower EC than healthy controls), but did not show elevated DU as in our prior sample. Follow-up analyses in specific disorder subgroups across the prior and current samples also provided further evidence that these effects were transdiagnostic and not specific to 1 substance use disorder or affective disorder.

Findings in substance use disorders are consistent with other computational work reporting lower levels of action precision (i.e., greater choice inconsistency) and slower learning from negative outcomes in this population;[49,50] they could also relate to previously observed blunting of brain and behavioural responses to affective stimuli[51,52] and lower self-reported sensitivity to punishment.[53,54] This

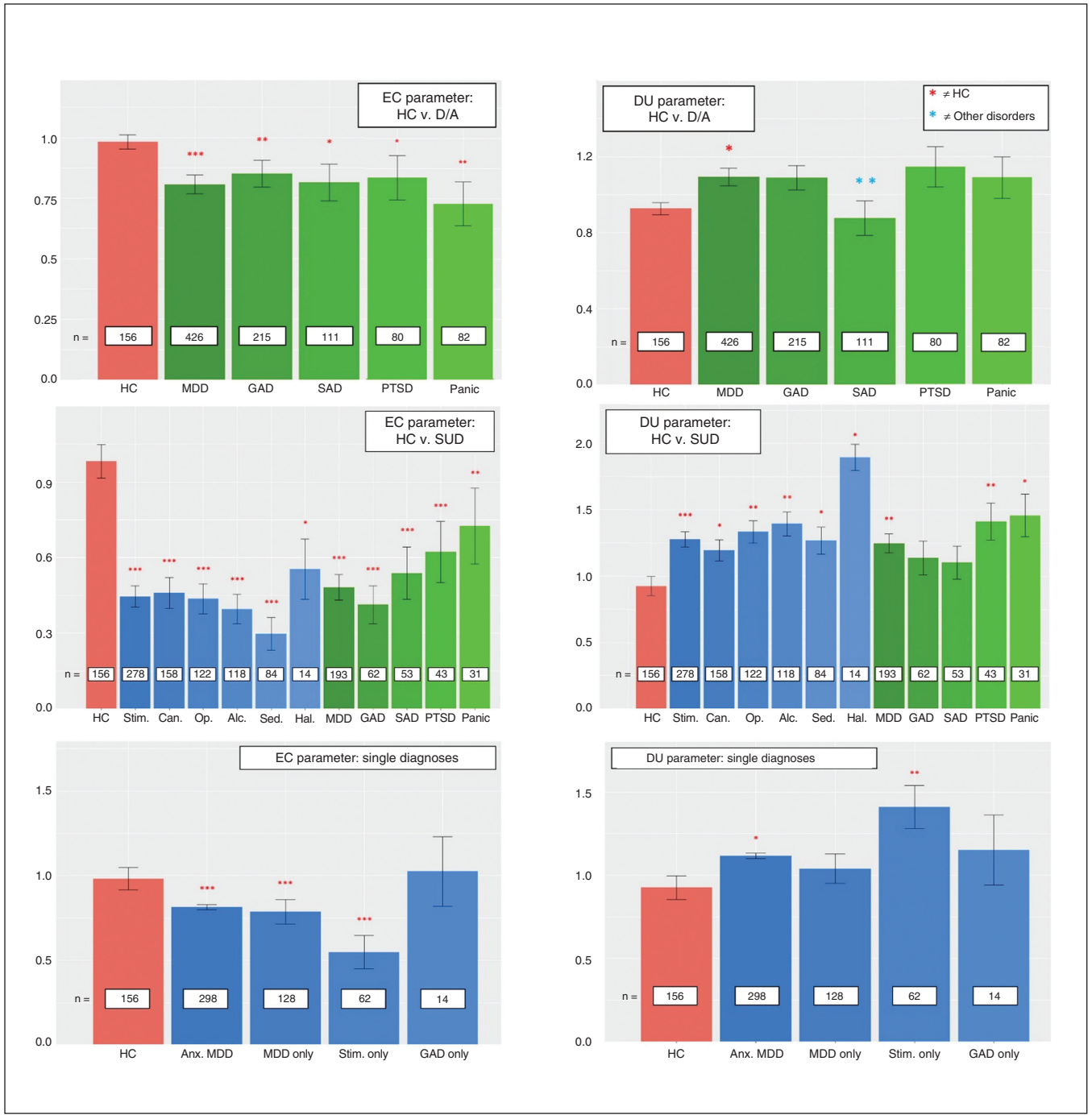

Figure 6: Comparison of healthy controls (HC) and subsets of individuals with specific affective disorders in the depression/anxiety disorder (D/A) group (top row) and with specific substance use disorders (SUD; middle row), some of whom also had affective disorders, within the combined exploratory and confirmatory data sets (sample size per group is indicated within each bar, based on groupings shown in Figure 1). Red asterisks indicate that, in logistic regressions, model parameters could predict whether individuals were healthy controls or had a specific disorder (i.e., removing individuals from analyses without the disorder in question), either including comorbidities (top 2 rows) or in individuals without comorbidities (bottom row; $*p < 0.05$, $**p < 0.01$, $***p < 0.001$). Individuals with depression and comorbid anxiety (Anx. MDD) have also been included in the bottom plots to compare with those with depression (MDD only) or generalized anxiety disorder (GAD only) alone. Blue asterisks indicate that model parameters could further predict whether an individual had one disorder relative to other disorders (i.e., removing healthy controls from analyses). Statistical results are reported in Appendix 1, Tables S10–S13, available at www.jpn.ca/lookup/doi/10.1503/jpn.220226/tab-related-content. Alc. = alcohol use disorders; Can. = cannabis use disorders; DU = decision uncertainty; EC = emotion conflict; Hal. = hallucinogen use disorders; Op. = opioid use disorders; PTSD = posttraumatic stress disorder; SAD = social anxiety disorder; Sed. = sedative use disorders; Stim. only = stimulant use disorders without comorbidities.

could therefore be part of a broader pattern of vulnerability in which drug-seeking behaviour is not deterred by either its anticipated or experienced negative consequences.

Findings in the depression/anxiety group provide support for a consistent (small to moderate effect size) reduction in avoidance drives (lower EC) among females, but they do not support the differences in DU suggested by our prior findings. However, the previous depression/anxiety sample was slightly older than the current sample, and there was also a positive association between age and DU. This age difference might therefore have contributed to lower DU values in the current sample. In addition, follow-up analyses in the combined sample suggested that social anxiety disorder was associated with lower DU than other affective disorders. As the proportion of individuals with social anxiety was higher in the current sample (Figure 1), this might also help explain differences in DU between depression/anxiety samples.

For EC, both this and our previous study found that differences were driven by females (i.e., only female healthy controls showed elevated avoidance relative to female depression/anxiety and all male groups, similar to previous work[55]). The replication of this sex difference suggests certain mechanisms underlying maladaptive decision-making under AAC may be more common in females. It also raises the possibility that such mechanisms could benefit from distinct interventions. The broad range of EC and DU scores seen in substance use disorders similarly suggests that different mechanisms (and therefore treatment targets) may be most relevant in different individuals. For example, cognitive bias modification methods that train increased avoidance in response to drug cues might be more helpful for those with low EC values,[56] while psychotherapeutic interventions focused on increasing treatment motivation or self-efficacy might be more helpful at decreasing DU in those with high DU values. Interventions that focus on enhancing awareness of one's actions and associated outcomes/consequences (i.e., interventions focused on mindfulness, planning or future thinking) might also be expected to selectively target DU in a similar manner (e.g., see[57–60]).

In repeating all analyses performed in our prior report, some findings that were not significant in the original study did show significant results in this sample. Most prominently, some significant differences in self-report measures seen here were not present in the prior sample, despite being highly consistent with the broader pattern of behavioural results. This could indicate differences in awareness or attention to task experiences between the current and previous samples. Future work might include measures of metacognitive awareness to further assess this possibility. However, as these findings were not present in both samples, they should be afforded less confidence until this ambiguity is addressed in future work.

It is worth highlighting that our computational phenotyping of these clinical cohorts was based on an active inference account of choice behaviour under uncertainty. This can be contrasted with simply testing for differences in choice behaviour or response times. For example, because one can explain differences in observable behaviour in terms of subjective (Bayesian) beliefs and preferences, this allows response time differences among participants to be linked to DU and associated belief updating. This follows because active inference implies that decision processes are approximately Bayesian, under particular (participant-specific) prior beliefs.[61,62] Notably, this class of models has a proposed, biologically plausible process theory that could afford examination of predicted neural correlates in future work. For example, DU rests on a prior precision parameter that has been associated with dopaminergic signalling on both theoretical and empirical grounds.[63,64] This may be interesting in relation to substance use disorders owing to the known links between drugs of abuse and dopamine dysfunction.[65] For example, based on prior fMRI studies using active inference,[63] one might expect altered activation within the midbrain and several striatal and cortical regions (e.g., dorsolateral prefrontal cortex) modulated by dopamine. Consistent with this, recent work has shown that our AAC task engages similar striatal and cortical regions.[34] However, it remains to be seen how this activation relates to individual differences in DU or how this activation is altered in substance use disorders.

Similarly, the EC parameter is defined in terms of the precision of preferences for affective stimulus outcomes, and this precision is also expected to be encoded by neuromodulatory processes. However, the specific neural circuits that modulate preference precision are not well-established, and our modelling approach could be used to help identify these circuits in future fMRI studies. Characterization of brain–body interactions contributing to attenuated affective avoidance drives may also be important, given previous work suggesting computational dysfunction in such processes (e.g., promoting reduced responsiveness to afferent signals) within both affective and substance use disorders (e.g., see[18,66,67]). This represents an important next step in establishing neurobiological mechanisms that could act as novel treatment targets.

Limitations

Some study limitations arose from our inability to perform planned analyses in propensity-matched subgroups, and from the substantial missing data on WRAT reading scores estimating baseline intellectual functioning. Most results remained significant in the subsample with WRAT reading scores, but we remain limited in our ability to determine the degree to which baseline intellectual functioning accounts for individual differences in some results. A related limitation is that WRAT reading scores differed between the previous and current samples. However, it is important to highlight that, even if baseline intellectual functioning relates to computational mechanisms, our results nonetheless highlight decision processes that may have more proximal explanatory power and/or clinical relevance (e.g., if DU and EC were more easily modified than

general intellectual functioning). A final issue worth mention is that, despite significant differences, there was still considerable overlap between groups in the distributions of DU and EC scores. This could indicate measurement error or important unmeasured influences on parameter values. However, it could also indicate heterogeneity within diagnostic groups (i.e., that different underlying processes may contribute to similar symptom profiles in different individuals). These considerations further highlight the importance of identifying the biological basis of these computational mechanisms as well as other important influences on their variation.

Conclusion

We successfully replicated and extended our previous findings in a second large community patient sample, providing further evidence for transdiagnostic effects. Reductions in EC were especially notable (and of potential clinical relevance) given their large effect size. As other studies have instead found evidence of increased avoidance in affective disorders (e.g., see[68]), it will be important to identify what the relevant differences are between the associated decision contexts. It will also be important for future studies to assess the degree to which EC and DU can be modified therapeutically in both affective disorders and substance use disorders for the purpose of achieving symptom improvement.

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Competing interests: M. Paulus is supported by the National Institute on Drug Abuse (U01DA050989). He is an advisor to Spring Care, Inc., a behavioural heatlh startup; has received royalties for an article about methamphetamine in UpToDate; and has a consulting agreement with and receives compensation from F. Hoffmann-La Roche Ltd. No other competing interests were declared.

Contributors: R. Smith took lead in analysis planning and writing the manuscript. C. Lavalley, S. Taylor, J. Stewart, H. Berg and M. Ironside helped perform analyses. All authors contributed to writing and reviewing the manuscript. R. Aupperle, M. Paulus and S. Khalsa contributed to the larger T1000 study design and data collection. All authors approved the final version to be published, agreed to be accountable for all aspects of the work and can certify that no other individuals not listed as authors have made substantial contributions to the paper.

Software note: All model simulations were implemented using standard routines (here spm_MDP_VB_X.m) that are available as Matlab code in the latest version of SPM academic software: http://www.fil.ion.ucl.ac.uk/spm/. Matlab code specifying the generative model of the AAC task can be found as supplementary material in Smith et al.[9]

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