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Intertemporal decision-making-related brain states predict adolescent drug abuse intervention responses

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ABSTRACT

Adolescent drug misuse represents a major risk factor for long-term drug use disorders. However, wide individual differences in responses to first-line behavioral therapies targeting adolescent drug misuse limit critical early intervention. Identifying the neural signatures of those adolescents most likely to respond to an intervention would potentially guide personalized strategies for reducing drug misuse. Prior to a 14-week evidence-based intervention involving combinations of contingency management, motivational enhancement, and cognitive behavioral therapy, thirty adolescent alcohol and/or cannabis users underwent fMRI while performing a reward delay discounting (DD) task tapping an addiction-related cognition. Intervention responses were longitudinally characterized by both urinalysis and self-report measures of the percentage of days used during treatment and in post-treatment follow-up. Group independent component analysis (ICA) of task fMRI data identified neural processing networks related to DD task performance. Separate measures of wholesale recruitment during immediate reward choices and within-network functional connectivity among selective networks significantly predicted intervention-related changes in drug misuse frequency. Specifically, heightened pre-intervention engagement of a temporal lobe "reward motivation" network for impulsive choices on the DD task predicted poorer intervention outcomes, while modes of functional connectivity within the reward motivation network, a prospection network, and a posterior insula network demonstrated robust associations with intervention outcomes. Finally, the pre-intervention functional organization of the prospection network also predicted post-intervention drug use behaviors for up to 6 months of follow-up. Multiple functional variations in the neural processing networks supporting preference for immediate and future rewards signal individual differences in readiness to benefit from an effective behavioral therapy for reducing adolescent drug misuse. The implications for efforts to boost therapy responses are discussed.

1. Introduction

Adolescence represents the developmental period most associated with the initiation of drug misuse and thus the heightened potential to develop drug use disorders (Degenhardt et al., 2016). In 2017, > 1 in 10 teens reported current illicit drug use and nearly 1 in 5 individuals between 12 and 20 years of age reported alcohol use in the past month (Substance Abuse and Mental Health Services Administration, 2018). Drug abuse among teens is associated with heightened risk for myriad adverse academic, health, cognitive, social, and legal outcomes (Volkow et al., 2014). An influential model posits that the development of addiction represents a brain-based learning process driven by early, repeated drug misuse experiences (Kandel and Kandel, 2015); indeed, adolescent drug misuse represents a major risk factor for long-term drug use disorders (Chambers et al., 2003; Stone et al., 2012). Adolescence thus represents the critical period for effective early intervention to halt emerging drug use behaviors and thus prevent their negative long-term outcomes (Henderson et al., 2019).

Recent intervention development initiatives targeting adolescent drug misuse have explored the use of motivational enhancement, contingency management and cognitive behavioral strategies implemented across individual, school, and family settings (Das et al., 2016; Stewart et al., 2015; Winters et al., 2014), but currently available interventions remain imperfect solutions. For cannabis, the most common drug of

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abuse related to teen treatment admissions (Substance Abuse and Mental Health Services (SAMSA, 2018), less than a quarter of adolescents were abstinent from cannabis use at the end of treatment with negligible differences in outcomes between different evidence-based interventions (Dennis et al., 2004). Clearly, intervention response is associated with substantial inter-individual variability, posing a major barrier to effective early intervention. Predicting those adolescents who will respond to a particular treatment remains a major goal of attempts to develop personalized strategies matched to individual variance in the mechanisms of treatment response.

Both evoked brain responses and states of functional brain organization can predict individual variability in treatment outcomes for drug use disorders (Courtney et al., 2016; Feldstein Ewing et al., 2013; Gowin et al., 2015; Moeller and Paulus, 2018). The reliable and accurate use of functional brain states to predict treatment responses for drug use disorders depends on targeting specific cognitive-behavioral states that exhibit close associations with drug use disorders and their response to intervention. One such candidate addiction-related cognition is the discounting of reward values by temporal delay in their receipt, a phenomenon referred to as delay discounting (DD) (Courtney et al., 2016; Kalivas and Volkow, 2005). Indeed, individuals with drug use disorders, including adolescents with problematic drug misuse (Audrain-McGovern et al., 2004; Field et al., 2007), exhibit exaggerated discounting rates (Bickel et al., 2007; MacKillop et al., 2011). Of direct relevance to this work, both adult (Coughlin et al., 2018; Washio et al., 2011; Yoon et al., 2007) and adolescent (Krishnan-Sarin et al., 2007; Stanger et al., 2011) substance users who are high discounters exhibit poorer treatment responses compared to those with lower discounting rates. We previously used fMRI to identify the neural processing networks related to individual differences in DD rates among adolescents entering treatment for misuse of cannabis and/or alcohol (Stanger et al., 2013). Our previous fMRI study as well as numerous others indicate that choices between smaller, sooner or larger, later rewards depend on neural systems involved in valuation, cognitive control, prospection, and motivational processes (Elton et al., 2016; Kable and Glimcher, 2007; McClure et al., 2004; Monterosso and Luo, 2010; Peters and Büchel, 2011; van den Bos and McClure, 2013). Given that these neural systems underlie a known behavioral predictor of addiction treatment outcomes (i.e., DD), the present study sought to identify DD task-related brain-based predictors of individual variability in adolescent intervention response.

In the current study, adolescents performed a fMRI DD task prior to beginning a 90-day outpatient combination therapy that included motivational enhancement and cognitive-behavioral therapy (Stanger et al., 2015; Stanger et al., 2017). With the intervention outcomes of the parent studies now available, we analyzed the fMRI data to inform the relationship between pre-intervention fMRI measures of DD and subsequent in-treatment and post-treatment outcomes. We tested the hypothesis that individual variation in the engagement and functional organization of neural processing networks related to immediate- and future-oriented decision preference predicts individual variation in response to this combination intervention. The results obtained support the contention that the identified neural predictors represent modifiable brain states relevant to predicting the individual intervention response of adolescents with emerging drug use disorders and their post-intervention drug misuse.

2. Methods

2.1. Participants

The thirty adolescent participants (aged 12–18, mean: 15.7 years; 6 females/24 males; 19 white/10 black/1 Hispanic) included in the current analysis were previously characterized in a report examining the neural correlates of individual variation in immediate- and future-oriented choice behavior (Stanger et al., 2013) and were participants in outpatient clinical trials assessing the impact of combination behavioral therapies for adolescent drug misuse. The current study examined the ability of these neural processing network correlates of decision-making within the DD task to predict therapy response.

Adolescents were enrolled in one of two studies investigating the behavioral and neural responses to weekly motivational enhancement/cognitive-behavioral therapy (MET/CBT), with some participants randomly assigned to also receive contingent management (CM) via incentives for documented abstinence. One study focused on alcohol misuse (Trial 1) and the other on cannabis misuse (Trial 2). Inclusion in Trial 1 ($n = 16$) required self-reported alcohol use in the last 30 days in addition to either meeting DSM-IV criteria at study entry for alcohol abuse or dependence ($n = 2$) or having engaged in at least one binge episode - defined as at least 5 alcoholic beverages in a 24-h period - in the past 90 days. Likewise, Inclusion in Trial 2 ($n = 14$) required self-reported cannabis use in the last 30 days or a positive urine test for THC in addition to meeting DSM-IV criteria for cannabis abuse or dependence ($n = 3$) at study entry. Notably, the majority (14/16) of those adolescents enrolled in Trial 1 reported cannabis use or evidenced a cannabis-positive urinalysis result at baseline despite the Trial 1 inclusionary criterion of being contingent on alcohol use (Stanger et al., 2017).

2.2. Intervention

The larger purpose of the two parent outpatient clinical trials was to test interventions designed to increase the efficacy of Motivational Enhancement Therapy combined with Cognitive Behavioral Therapy (MET/CBT) for reducing problematic drug use among clinically-referred substance-misusing youth. Study procedures were similar across both studies/trials and have been described in detail previously (Stanger et al., 2015; Stanger et al., 2017). All adolescents in Trial 1 (Stanger et al., 2017) and Trial 2 (Stanger et al., 2015) received 14 weeks of MET/CBT (Sampl and Kadden, 2001; Webb et al., 2002). Additionally, adolescents were randomly assigned to receive an abstinence-based contingency management (CM) intervention, which involved a combination of clinic and home-based monetary incentives for abstinence from all substances, or no CM. Adolescents in Trial 2 randomized to receive CM were also randomized to receive either a parent training (PT) intervention, which targeted conduct problems, or no PT. Independently rated fidelity to MET/CBT was acceptable for the parent clinical trials (Stanger et al., 2015; Stanger et al., 2017).

Subjects participating in the parent treatment trials (Stanger et al., 2015; Stanger et al., 2017) were given the option to enroll in the neuroimaging study. The primary goal of the present study was to define those neural correlates of intertemporal decision making that significantly predict subsequent treatment response while retaining the primary clinical trial focus on MET/CBT. The current sample of adolescents received MET/CBT ($n = 11$), MET/CBT + CM ($n = 3$), or MET/CBT + CM + PT ($n = 16$). Negative breathalyzer tests for recent alcohol use were required on the day of the scan and negative results were obtained for all participants. Some participants submitted drug positive urine specimens on the day of the scan, but positive samples did not exclude individuals from participation. Detailed subject characteristics, including demographics, drug use, and psychiatric diagnoses are provided in Supplemental Table 1. The Institutional Review Board (IRB) of the University of Arkansas for Medical Sciences approved both trials and this neuroimaging study.

Both trials demonstrated statistically significant decreases in cannabis use during the intervention based on the full sample ($n = 153$) with larger effects for MET/CBT + CM (with or without PT) than MET/CBT alone (Stanger et al., 2015; Stanger et al., 2017). The addition of the PT intervention was not associated with additional reductions in cannabis use compared to MET/CBT + CM (Stanger et al., 2015). Furthermore, because study procedures were essentially identical for the two trials and participants from both trials were eligible to

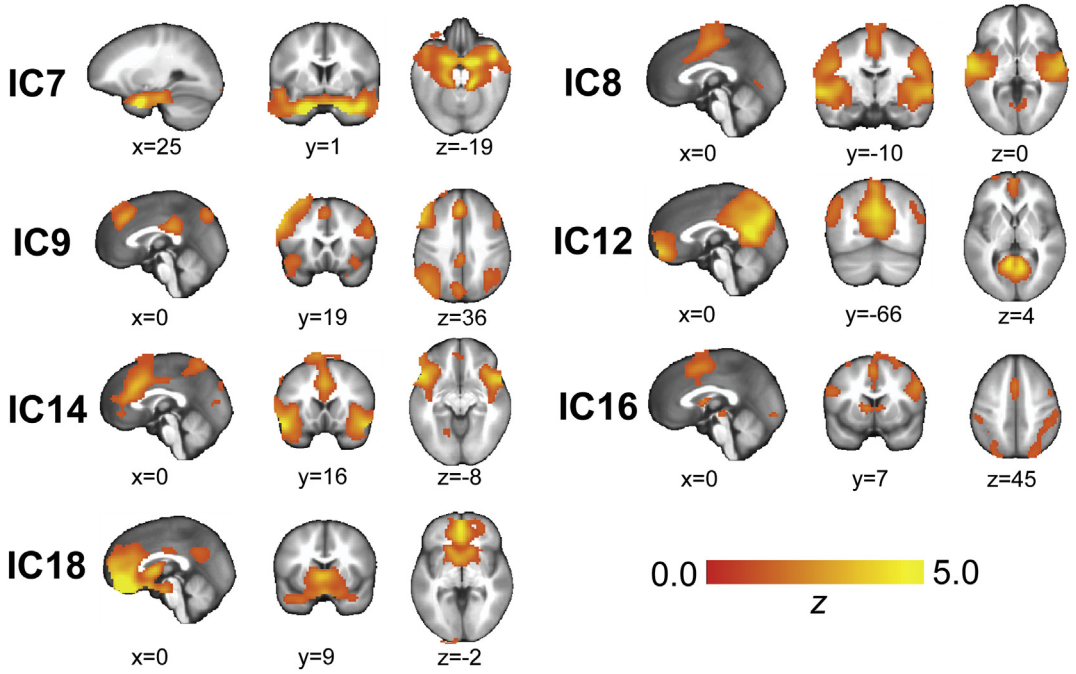

Fig. 1. Representative sagittal, coronal, and axial sections depicting each independent component tested for functional association with intervention-related changes in drug misuse. Positive values, z ≥ 1.0, are overlaid on anatomical images.

participate in the neuroimaging study, we analyzed the pooled sample.

2.3. Pre-treatment, in-treatment, and post-treatment measures of drug misuse

Two separate measures of intervention effects on drug misuse frequency based on objective urine and breath analysis and subjective self-report were collected as treatment outcome variables. Urine testing and alcohol breathalyzer tests were performed once-weekly (Trial 1, $n = 16$) or twice-weekly (Trial 2, $n = 14$) throughout the 14-week treatment period. The percentage of drug-positive samples was defined as the total number of alcohol-positive breathalyzer tests or positive urinalyses outcomes for multiple drugs of abuse – including cannabis, cocaine, opioids, benzodiazepines, amphetamines, methamphetamines and alcohol (based on detection of urine ethyl glucuronide (EtG)) – divided by the total number of breath or urine analyses performed. Failure or refusal to provide a urine or breath sample was coded as a positive test, as were self- or parent-reports of use. The percentage of days of self-reported substance use during the intervention period was assessed at the end of treatment using the Time-Line Follow Back (TLFB (Sobell and Sobell, 1992)) for alcohol, cannabis, and other illicit substances. Similarly, pre-treatment TLFB assessments of the previous 90 days of drug misuse were conducted at study intake (baseline percentage of days used) and at each of three post-intervention follow-up time points. For the pre-intervention and post-intervention assessments of drug misuse severity, the percentage of days used was calculated as the number of self-reported days of any drug use divided by the number of days for each data collection period.

2.4. Delay discounting (DD) task and behavioral analysis

As previously reported, the fMRI DD task was modeled as an event-related design. Subjects made choices between varying hypothetical smaller, sooner (SS) monetary rewards offered "today" and a hypothetical fixed larger, later (LL) reward ($1000) offered at one of four temporal delay intervals (1 month, 6 months, 1 year, and 5 years). In control (CON) trials, subjects selected between two monetary amounts offered "today" to provide a contrast condition controlling for non-temporal monetary decision processes, motor responses, and attention. There were 20 trials for each delay, as well as 20 CON trials. Monetary values for SS rewards were individually varied around the participant's indifference point initially defined by a prior DD task and adjusted online based on responses.

Individual discounting rates (k) were estimated from decision preferences obtained by a computerized DD task version administered prior to the MRI scan, as described previously (Stanger et al., 2013). Higher k values indicate greater DD (i.e. decreasing reward value with increasing delay to receipt). K values were assessed for correlation with the two intervention response measures (i.e., percent days used and percent positive urine/breath samples) using Spearman partial correlation analyses, controlling for age, sex, study (Trial 1 versus Trial 2), treatment arm, and the percentage of self-reported days of use during the 90-day pre-intervention period.

2.5. Image acquisition and preprocessing

As previously described (Stanger et al., 2013), DD task-related BOLD and MPRAGE sequences were acquired and fMRI data pre-processed prior to analysis. These experimental approaches are detailed in the Supplemental Materials.

2.6. Independent component analysis (ICA)

We previously conducted a group ICA of all 30 subjects' DD task fMRI data using the Group ICA of fMRI Toolbox (GIFT (Calhoun et al., 2001)) in MATLAB, and then related individual DD rates to recruitment of independent component (IC)-represented brain networks (Stanger et al., 2013). The current analyses utilized this previous ICA solution, in which we solved for 20 ICs. From the 20 ICs, we previously selected seven for further investigation of their intervention response relatedness based on their reported canonical roles in higher-order task processes (Stanger et al., 2013). We further investigated these same seven networks in the current study (Fig. 1), thus facilitating comparisons and inferences across studies. These ICs are also highly consistent with those previously reported in other neuroimaging studies, including those utilizing healthy adult populations and resting state data (e.g., Smith

Table 1
Drug misuse variables defined by self-report of days used versus urinalysis for each data collection period.

In-treatment	Days used any drug	Positive UA, any drug	Days used alcohol	Positive alcohol UA	Days used cannabis	Positive cannabis UA
Mean	18%	47%	5%	23%	14%	42%
SD	*27%*	*37%*	*10%*	*29%*	*26%*	*37%*
Pre-treatment	Days used any drug		Days used alcohol		Days used cannabis	
Mean	34%		7%		28%	
SD	*29%*		*11%*		*27%*	
Post-treatment	Days used any drug: 0–3 months	Days used any drug: 3–6 months	Days used any drug: 6–9 months			
Mean	13%	20%	23%			
SD	*21%*	*29%*	*27%*			

et al., 2009; Zuo et al., 2010), attesting to the potential for the current study findings to be reproducible and translational across studies. Spatial-temporal regression analysis conducted in GIFT provided subject-specific spatial maps and time series for each component, which were z-score normalized.

2.7. Identification of the relationships between wholesale IC engagement and intervention response

Previously, we used general linear modeling (GLM) to test the functional association of each IC-defined neural processing network with each DD task decision option (e.g., SS, LL, CON) and their planned contrasts (i.e., SS-CON, LL-CON) (Stanger et al., 2013) (see Supplemental Materials for detailed description of these analyses). The current work uniquely extends the prior analyses (Stanger et al., 2013) by testing the relationship between DD task-related recruitment of ICs and subsequent individual intervention responses. In separate tests for each of the seven selected ICs, SS-CON and LL-CON contrast values were assessed for correlation with both drug use outcome variables. Due to the non-normal distributions of the intervention response variables, Spearman's rank-order partial correlation coefficients were calculated, controlling for potential confounding variables including age, sex, study (Trial 1 versus Trial 2), treatment arm (MET/CBT or MET/CBT + CM), and the percentage of self-reported days of substance use in the 90-day pre-treatment period. Bootstrapping (10,000 iterations) of these correlations provided 95% confidence intervals (CI) and *p*-values of their significance. Significant ($p < .05$) correlations after false discovery rate (FDR (Benjamini and Yekutieli, 2001)) correction for all comparisons (28 comparisons: 7 components, 2 outcome variables, 2 contrasts) are reported.

2.8. Variable selection for IC functional connectivity analysis

In a second, independent analysis, we tested whether individual differences in the functional organization, rather than wholesale recruitment, of any of the DD task-related neural processing networks predicted adolescent treatment response. Participant-specific IC spatial maps of voxel-wise component scores representing the magnitude of each voxel's contribution to the IC were generated in GIFT; values represent the extent to which an individual voxel is recruited into the larger functional network, a reflection of network functional connectivity. We tested a hypothesis that individual differences in the voxel-level functional organization of particular ICs could predict individual variability in subsequent intervention responses. We tested this hypothesis using elastic net regularization (Zou and Hastie, 2005), an adaptation of stepwise regression, to identify the subset of voxel-wise component scores that optimally predicted intervention response as defined by the study drug use variables.

We specifically examined the relationship of component scores within each subject's IC spatial maps (i.e., functional connectivity) to the two intervention response variables, performing separate analyses for each of the drug misuse measures. A detailed description of the elastic net regression procedure is provided in the Supplemental Materials. Importantly, we partialled out the percentage of days of reported substance use in the 90-day pre-treatment period from the in-treatment drug use measures prior to analyses to ensure that analyses captured individual differences in intervention-related effects rather than differences related to the pre-intervention severity of drug misuse. For the seven selected ICs, we used a leave-one-out cross validation (LOOCV) procedure to identify sets of IC voxels predicting each response varaible and assess their prediction reliability and accuracy (see LOOCV details in the Supplemental Materials). Significant ($p < .05$) results after an FDR correction for all comparisons (14 comparisons: 7 components, 2 outcome variables) are reported.

2.9. Post-hoc analyses of IC predictor variables for the post-intervention period

For those statistically significant relationships between intervention response and either IC engagement or connectivity identified in the main analyses, *post-hoc* Spearman's correlations considered their further predictive relationship to TLFB-based drug use at three post-intervention follow-up time points (3 months, 6 months, and 9 months). This follow-up extension determined whether pre-intervention predictors of in-treatment changes in drug misuse behaviors were similarly predictive of post-treatment drug misuse behavior. Two subjects were missing follow-up data at all three time points and were eliminated from analysis, and one additional subject was missing data for the 9-month follow-up only.

3. Results

Participant drug misuse variables are summarized in Table 1. For the two measures, Spearman correlation indicated that the self-reported percentage of days of drug use was highly correlated with the percentage of drug-positive urine/breath tests throughout treatment ($\rho = 0.74$, $p < .001$). Only five adolescents reported complete abstinence from drugs of abuse for the duration of the treatment period; of those, four consistently provided drug-free urine samples during that time.

3.1. Behavioral analysis

Spearman partial correlation analyses indicated that pre-treatment DD task-defined *k* values did not significantly correlate with the percent days of self-reported drug use ($\rho = 0.07$, $p = .74$) or percent positive urine samples ($\rho = 0.32$, $p = .11$) during treatment.

Table 2
Independent component (IC) coordinates.

Region	*x*	*y*	*z*	*Peak z-score*	*n voxels*
IC 7					
Left amygdala	-12	-4	−26	6.44	3626
Right temporal polar cortex	33	11	−29	6.27	(multiple peaks)
Left parahippocampal gyrus	−16	−28	−21	4.54	
Right parahippocampal gyrus	17	−25	−24	4.20	
Left temporal polar cortex	−42	8	−26	3.70	
Medial prefrontal cortex	0	41	1	1.24	
IC 8					
Right superior temporal gyrus	60	−10	1	4.10	2409
Left superior temporal gyrus	−60	−16	7	4.04	2256
Pre-supplementary motor area	0	−7	52	2.44	907
Left lingual gyrus	−9	−61	1	1.16	54
IC12					
Posterior cingulate cortex, precuneus	0	−55	16	5.14	4085
Ventromedial prefrontal cortex, orbitofrontal cortex	3	56	−8	3.86	554
Right angular gyrus	45	−70	34	1.88	450
Left angular gyrus	−42	−76	31	1.76	224
Right superior frontal gyrus	30	38	49	1.67	83
Left frontal pole	−24	−65	13	1.57	27
Right frontal pole	27	65	4	1.19	27
Left superior frontal gyrus	−27	38	52	1.30	20

3.2. ICA analysis

Spatial maps of each of the seven ICs included in the analyses are displayed in Fig. 1. These maps are displayed with a z-score threshold of 1.0, representing the voxels included in the mask for the functional connectivity analysis. It should be noted that IC engagement analyses utilized time series that were derived from the entire whole-brain dataset, rather than a subset of voxels, using the spatial-temporal regression technique (Stanger et al., 2013; Zuo et al., 2010).

3.3. Relationship of level of wholesale IC engagement and intervention response

One IC demonstrated a significant relationship between its level of pre-treatment recruitment during choices of immediate rewards (SS-CON contrast) and rates of drug misuse during treatment. Greater decision-making-related engagement of IC7, a functional network encompassing the ventral medial temporal lobe, temporal poles, and ventromedial prefrontal cortex (Stanger et al., 2013) (Fig. 1, Table 2), during impulsive decisions favoring immediate rewards predicted poorer subsequent intervention responses. Specifically, the individual level of engagement of this ventral temporal-prefrontal network during SS choices exhibited a positive correlation with both the percentage of drug-positive urine/breath samples ($\rho = 0.56$; 95% CI: [0.30, 0.75], $p = .002$) and with the percentage of self-reported days of drug use ($\rho = 0.67$; 95% CI: [0.44, 0.84], $p < .001$) during treatment. Correlations between pre-treatment recruitment of IC7 during LL trials for either treatment outcome variable did not survive an FDR correction for multiple comparisons. Scatter plots of these relationships are displayed in Fig. 2A-B. No other ICA-derived network significantly correlated with intervention response based on their level of recruitment during either LL or SS trials after FDR correction.

3.4. Relationship of intrinsic network connectivity to in-treatment outcomes

Three neural processing networks demonstrated patterns of pre-treatment functional organization that predicted later individual intervention response. The functional organization of IC7 predicted the percentage of drug-positive urine samples during treatment ($\rho = 0.72$, $p < .001$; Fig. 3A). Individual functional connectivity of a second component, IC8, for which peak component scores were present bilaterally in posterior insula and lateral temporal lobes, and in the pre-SMA and left lingual gyrus (Fig. 1, Table 2), was also related to the percentage of drug-positive urine samples during treatment ($\rho = 0.73$, $p < .001$; Fig. 3B). The pattern of functional organization of a third network represented by IC12, which demonstrated close anatomical alignment with the "default-mode network" (Raichle, 2015) (DMN) (Fig. 1, Table 2), predicted both the percentage of drug-positive urine/breath samples ($\rho = 0.55$, $p = .002$; Fig. 3C) and the percentage of self-reported days of in-treatment drug use ($\rho = 0.60$, $p < .001$; Fig. 3D). No other tested ICs significantly predicted intervention outcomes based on their intrinsic functional connectivity following FDR correction ($\alpha = 0.05$).

To identify the specific modes of predictive network functional organization, we examined the neuroanatomical locations of the voxel-level functional connectivity predictors within the three ICs that predicted intervention responses. Because each iteration of the LOOCV produced a different predictor (i.e., different combinations of voxels), for each network we illustrated results as t-statistics from univariate one-sample *t*-tests at each voxel, which statistically quantified the strength, direction, and consistency of voxel predictor values across all 30 LOOCV iterations (Fig. 3E). These brain maps are not to be interpreted in a similar manner as typical univariate statistical parametric maps in which statistical significance and cluster size thresholds are applied. In contrast to typical univariate approaches, elastic net selects from voxels across the entire brain and the resultant predictor considers the selected voxels in combination. Furthermore, elastic net uses a sparse selection of voxels for each predictor, meaning few voxels across correlated brain regions may be selected even if many voxels are associated with the outcome variable. Thus, larger clusters simply indicate that neighboring voxels were variably selected across iterations of the LOOCV, whereas greater t-statistics in this map indicate that a particular voxel was selected consistently across iterations and/or demonstrated strong predictive values when selected.

Multiple patterns of functional connectivity predictors of within-intervention drug misuse within IC7 were observed. The functional connectivity of voxels within the temporal poles, medial temporal lobe, cerebellum, and ventromedial prefrontal cortex of IC7 contributed to prediction of drug misuse, with both positive and negative associations observed within these network regions. For this IC, the largest clusters of predictor voxels were located in the right (peak voxel: $x = 36$, $y = 14$, $z = -32$) and left (peak voxel: $x = -33$, $y = 23$, $z = -26$) inferior temporal poles (Fig. 3E), and the predictor coefficients for those voxels suggested that greater within-network functional connectivity of these voxels was associated with reduced drug misuse. In other words, the greater the functional integration of the inferior temporal poles into the ventral temporal-prefrontal neural processing network represented by IC7, the better the adolescent response to the combination intervention.

Functional connectivity predictors within IC8 also exhibited both negative and positive relationships with drug use during treatment (Fig. 3E). Greater functional connectivity of large clusters of voxels within right posterior insula (peak voxel: $x = 48$, $y = -4$, $z = 7$) and left superior temporal sulcus (peak voxel: $x = -66$, $y = -22$, $z = 1$) for this insula-temporal-preSMA network predicted greater drug use (poorer intervention response). Conversely, greater functional connectivity within IC8 of a voxel cluster in the premotor cortex (peak voxel: $x = 3$, $y = -16$, $z = 73$) was associated with better intervention response.

For illustration purposes, voxel predictors within IC12 were merged for the two significant intervention outcome variables by calculating a single t-statistic across all 60 LOOCV iterations (30 for each predictor) using a one-sample test at each voxel (Fig. 3E). The largest clusters of predictive voxels for this DMN representation were located in the

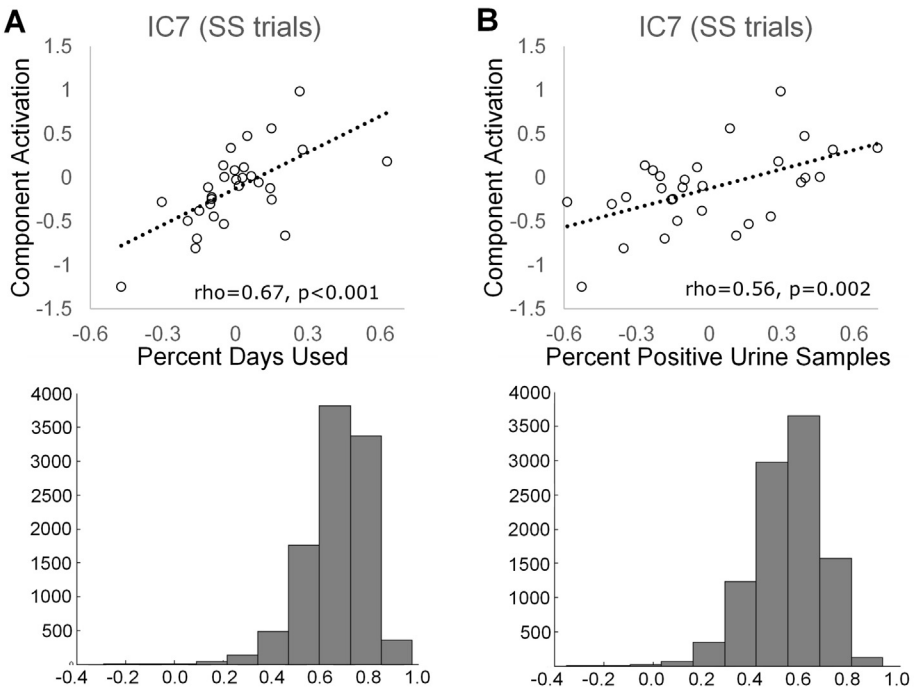

Fig. 2. Relationship of level of engagement of independent component 7 (IC7) related to choices for immediate rewards and within-intervention drug misuse. Scatter plots demonstrate significant correlations between engagement of IC7 during smaller, sooner (SS) decisions and both A) the percentage of days of self-reported drug use according to timeline follow-back calendars and B) the percentage of drug-positive urine samples during the intervention. Drug use variables represent residuals after adjusting for age, sex, trial, treatment arm, and percentage of self-reported days used in the 90-day pre-intervention period. Below each scatterplot, histograms depict the bootstrapped distributions of variable correlations.

ventromedial prefrontal cortex/medial orbitofrontal cortex (OFC) (peak voxel: x = −3, y = 38, z = −14) and dorsal precuneus (peak voxel: x = −6, y = −79, z = 31), for which their greater functional connectivity within IC12 was associated with greater drug use during treatment, and in the ventral posterior cingulate cortex (peak voxel: x = −6, y = −46, z = 1), which predicted intervention-related decreases in drug use.

3.5. Post-hoc tests of the accuracy of IC predictors of post-intervention drug use

Post-hoc analyses of the relationship between IC predictors of intervention outcomes and the percentage of days of self-reported drug use in the previous 90 days at three post-intervention follow-up time points (3 months, 6 months, and 9 months) based on TLFB are tabulated in Supplemental Table 3. Although the neural predictors of in-treatment changes in drug use were generally weak predictors of drug use at follow-up, significant relationships were detected for IC12 (i.e., DMN) functional connectivity. IC12 functional connectivity predictors of in-treatment drug urinalysis results also predicted the percentage of days of any drug use at 0–3 months ($\rho = 0.46$, $p = .02$) following treatment, whereas IC12 functional connectivity predictors of in-treatment self-reported drug use significantly predicted the percentage of days of drug use for 0–3 ($\rho = 0.42$, $p = .04$) and 3–6 months ($\rho = 0.48$, $p = .02$) post-intervention.

4. Discussion

Adolescence represents both the developmental period of origin of drug use disorders and the best opportunity for early preventive intervention and thus this developmental stage has particular significance to addiction research. We sought to identify the engagement and organization states of specific neural information processing networks related to preference choices for immediate versus future rewards that predicted the well-recognized individual differences in adolescent drug misuse behaviors over the course of both treatment and long-term follow-up. This study sought to address whether functional states of brain organization related to an addiction-related cognition were capable of predicting subsequent response of at-risk adolescents to combination behavioral therapies. Our findings indicate that both the level of wholesale recruitment and functional organization of neural processing networks involved in intertemporal decision-making significantly predict subsequent intervention-related changes in adolescent drug misuse (Fig. 4). These network states exhibited greater predictive power than did individual DD rates. This study informs strategies to prevent drug use disorders among adolescents at-risk for drug use disorders due to already initiated drug misuse by identifying those decision-related functional brain states that signal individual variation in likelihood of responding to evidence-based interventions.

A ventral temporal-prefrontal neural processing network (IC7) predicted subsequent intervention outcomes through both its variation in intrinsic functional connectivity and level of wholesale recruitment during present-oriented choices associated with impatience (van den Bos et al., 2015). Within the same study sample, greater engagement of this “reward motivation” network was previously associated with greater impulsivity represented by steeper discounting of delayed rewards (Stanger et al., 2013). These results suggest a brain state representation of the reported behavioral associations between a heightened preference for immediate rewards (i.e., high temporal discounters) and poorer drug abuse treatment outcomes among adolescent drug abusers (Krishnan-Sarin et al., 2007; Stanger et al., 2011), though this behavioral relationship (i.e., correlation with *k* values) was not observed in this subsample. The functionally connected brain regions comprising this ventral temporal-prefrontal network of activation included several limbic-paralimbic regions implicated in stimulus-reward associations (Boorman et al., 2016; Murray, 2007; Stanger et al., 2013): bilateral amygdala, bilateral hippocampus, bilateral ventral temporal poles, and ventromedial prefrontal cortex. The study results suggest that greater recruitment and particular patterns of functional connectivity organization for a network that biases decision choices toward immediately available rewards predispose drug-abusing adolescents toward poorer intervention responses. Strategies to override the neural responses to reward-predicting cues may help curb impulsive decisions to engage in drug use.

The functional connectivity of a cingulate-frontal-parietal network (IC12) during choice preferences for future rewards predicted both subsequent within-intervention and post-intervention drug use frequency. Neuroanatomically, this IC closely corresponds to the default-

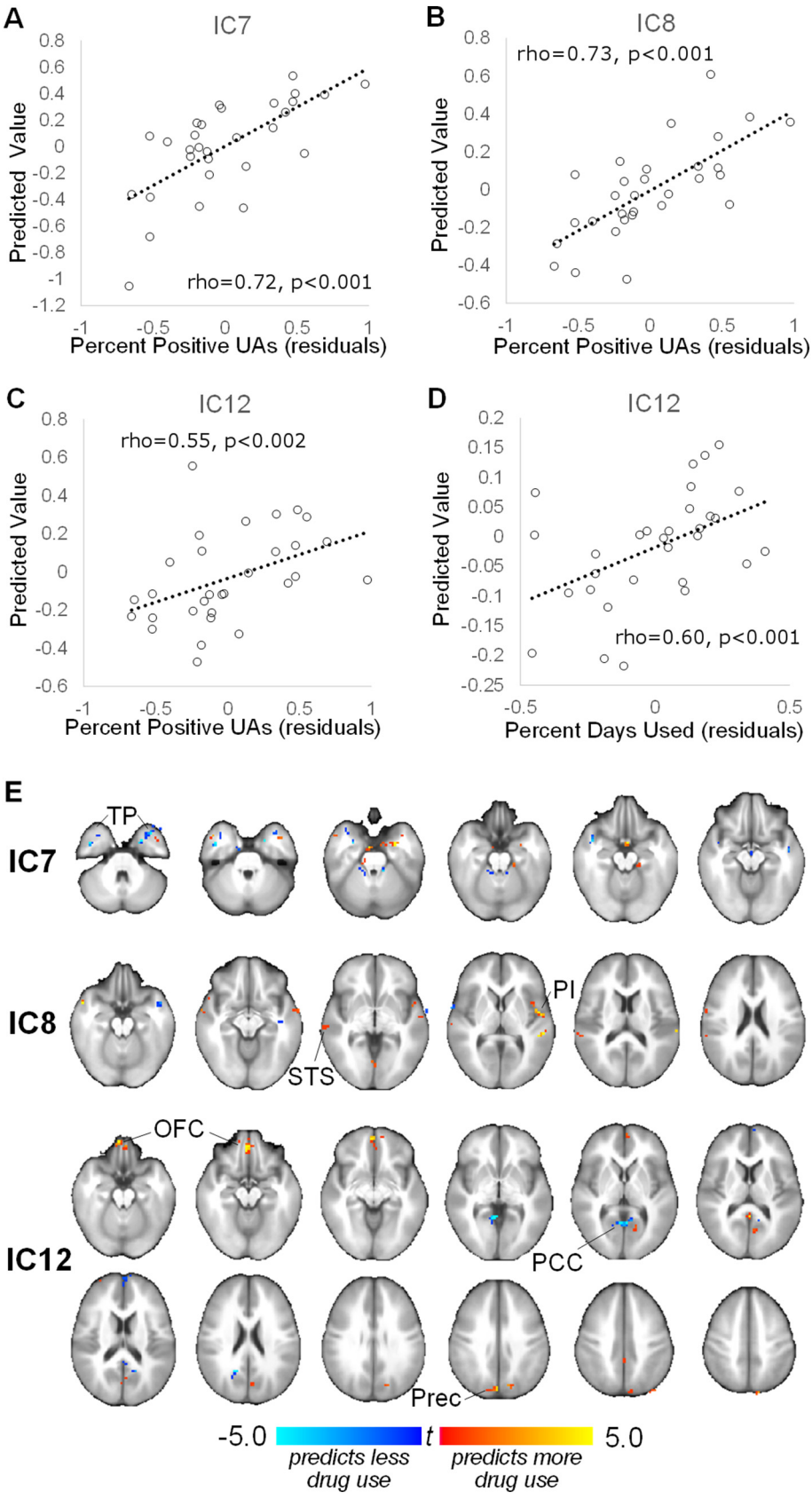

Fig. 3. Relationship between within-network functional connectivity predictors of within-intervention rates of drug misuse and actual rates of misuse. Scatter plots demonstrate significant correlations between the actual percentage of drug-positive urine samples during the intervention and predicted percentages of drug-positive urine samples based on functional connectivity patterns within A) IC7, B) IC8, and C) IC12. D) The percentage of days of self-reported drug use according to timeline follow-back calendars was similarly significantly correlated with the prediction of those outcome values by functional connectivity pattern within IC12. Drug use variables represent residuals after adjusting for age, sex, study, treatment arm, and the percentage of self-reported days used in the 90-day pre-intervention period. E) Visualization of functional network organization predictors of intervention outcome. To visualize and interpret the three independent components for which voxel functional connectivity predicted intervention responses, univariate one-sample *t*-tests were performed on the predictor coefficients at each voxel across all 30 LOOCV iterations to statistically quantify the strength, direction, and consistency of voxel predictor values. Unthresholded maps of the t-values of voxels within each IC identified as functional connectivity predictors across the 30 LOOCV iterations are displayed. For visualization purposes, voxel predictors within IC12 were merged for the two intervention outcome variables by calculating a single t-statistic using a one-sample test at each voxel. Warm colors represent predictors of greater drug use (poorer intervention outcomes) whereas cool colors represent reduced drug use (improved intervention outcomes). TP, temporal pole; STS, superior temporal sulcus; PI, posterior insula; OFC, orbitofrontal cortex; PCC, posterior cingulate cortex; Prec, precuneus.

mode network (Raichle, 2015), particularly its posterior subsystem or pDMN (Andrews-Hanna et al., 2010). The functionally connected brain regions comprising IC12 included the ventral posterior cingulate cortex, ventromedial PFC, bilateral angular gyrus, bilateral DLPFC, and rostral PFC. The DMN is consistently engaged by tasks that demand self-referential thought (Raichle, 2015; Spreng, 2012; Spreng et al., 2009). One such attributed role of the pDMN with direct relevance to the DD task is in prospection (Spreng et al., 2009; Xu et al., 2016), a process of

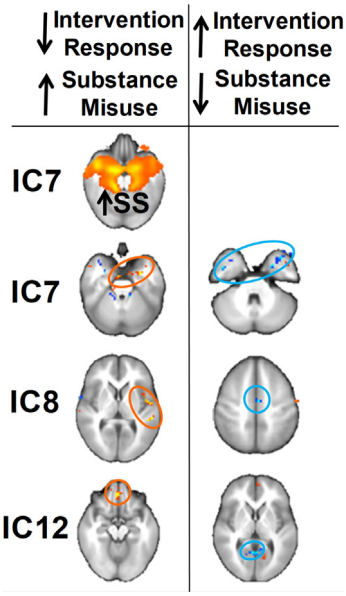

Fig. 4. Summary of independent component predictors of intervention response among adolescent drug misusers.

cognitive projection into one's future that is engaged during future-oriented choice behaviors (Benoit and Schacter, 2015; Stawarczyk and D'Argembeau, 2015). The ability to mentally simulate and pre-experience future decision outcomes has adaptive advantages in biasing present decision choices away from the greater incentive value of immediate gratification (Luo et al., 2009) and in favor of possible advantageous future outcomes (Bar, 2010). Indeed such episodic future thinking promotes real-world, health promotion decisions (Dassen et al., 2016; Kahana et al., 2005; Kaplan et al., 2016) and has been consistently associated with substance use behaviors (Bickel et al., 2007; MacKillop et al., 2011).

These prospection processes predict temporal discounting rates among adolescents (Bromberg et al., 2015) and are supported by DMN functional connectivity in both adolescents (van den Bos et al., 2015) and adults (Bellana et al., 2017; Peters and Buchel, 2010). Across adolescence, the DMN exhibits increasing connectivity within DMN subnetworks and decreasing connectivity between DMN subnetworks (Joshi et al., 2017; Sherman et al., 2014). Interestingly, greater functional integration of the anterior vmPFC/medial OFC and dorsal precuneus within the pDMN in this sample predicted poorer intervention responses for the targeted behavior of drug misuse. The dorsal precuneus, which is involved in behavioral engagement (Zhang and Li, 2010) and detects the possibility of an immediate reward (Albrecht et al., 2013), is not considered a core part of the DMN (Yang et al., 2014). Likewise, the anterior vmPFC contributes to the perception and processing of the experiential goal value of rewards (Hare et al., 2009) and immediate rewards for one's self (Albrecht et al., 2013). In contrast, greater functional integration of the ventral PCC, a hub region of the DMN, was associated with improved intervention response. This pattern of variation in PCC and medial OFC functional integration within IC12 may represent individual differences in DD decisions based on the relative allocation of DMN function between prospective versus reward-seeking processes. Indeed, compared to young adults, the greater preference for immediate rewards on a DD task among adolescents was related not to a predicted heightened sensitivity for immediate rewards but to poorer future orientation (Bromberg et al., 2015). The observed association of intervention response with a pattern of functional connectivity within a network supporting prospection suggests that a developmental immaturity in future orientation thinking (Bromberg et al., 2015) represents a barrier to early intervention to halt the addiction process among at-risk adolescents.

Within a posterior insular-temporal-preSMA network (IC8), the level of functional integration of the posterior insula, superior temporal gyrus, and SMA also predicted within-intervention changes (positive and negative) in drug misuse behaviors. Activation of a similar ICA-derived posterior insula-temporal network was previously associated with impulsive choices in an fMRI DD task among healthy adults (Elton et al., 2016). In that study, network engagement was interpreted as biasing decisions based on the visceral responses to reward choices. The morphology of the posterior insula has also been linked to addictive behaviors, an association that is mediated by DD (Turel et al., 2018). The association of stronger connectivity among the posterior insula and superior temporal sulcus regions of IC8 with poorer intervention response in the current study is consistent with individual variation in the extent to which one's drug misuse decisions are biased by interoceptive (or perhaps social (Lahnakoski et al., 2012; Turel et al., 2018)) associations with immediately gratifying, but ultimately less advantageous, reward expectancies among adolescents. Conversely, the observed association of increasing functional connectivity of the premotor cortex within IC8 with better intervention response is consistent with the abstinence-promoting effect of an increased influence on reward choice of a key region implicated in controlled action selection (Zapparoli et al., 2017). In the net, these findings for IC8 support the notion that individual differences in adolescent intervention response reflect individual variation in the modes of influence on drug use decisions of nodes reflecting differing information representations within a single network.

This study of functional brain states that predict individual differences in adolescent intervention response also sought to assess their endurance of prediction beyond treatment completion. For the self-reported percentage of drug use days during post-treatment follow-up, the functional connectivity of IC12 significantly predicted drug misuse behavior up to 6 months post-treatment. These sustained predictive relationships suggest that the cognitive style of intertemporal decision-making encoded within specific patterns of functional organization of the pDMN reflect individual predispositions for long-term responses to treatment. The association of this network with post-treatment drug misuse supports the potential value of adjunctive training of DMN functions – perhaps preferentially related to episodic future thinking (e.g., (Jing et al., 2017)) – to boost sustained responses to evidence-based interventions.

Though the study yielded interesting inferences, their strength is tempered by limitations of the study design. First, this study tested hypotheses regarding IC engagement and IC functional connectivity across seven ICs, two different measures or substance use and, in the case of the engagement analysis, two different decision types. Therefore, multiple comparisons corrections that encompassed each of these full sets of comparisons were required. As a result, the study was only powered to detect very robust effects. Furthermore, the lack of a control group of non-drug misusing adolescents precludes a comparison to normative modes of network functional organization that represent individual intertemporal choice preferences. Additionally, the brain state predictors were developed from within-intervention drug use measures. Future studies should also consider developing specific predictors of sustained post-intervention-related changes in drug misuse. Also this adolescent sample varied in the severity of their pre-intervention drug misuse with 5 adolescents fulfilling DSM-IV criteria for drug dependence. This variance is likely associated with varying alterations in functional brain organization that may not have been fully accounted for by controlling for pre-treatment variation in drug misuse frequency. A possible additional source of heterogeneity within the sample was the different intervention types within the combined intervention model (Stanger et al., 2015). However, all adolescents received individual therapy (MET/CBT) of demonstrated effectiveness and varied only in whether that intervention was accompanied by abstinence-based incentive (CM); though also stratified across the sample, parent training (PT) intervention affords negligible additional

intervention benefit (Stanger et al., 2015; Stanger et al., 2017). Finally, the sample of 30 adolescents was mixed on the potentially important variables of sex and types of drugs misused and lacked power to reliably discriminate their individual contribution to study outcomes.

In conclusion, results from this individual differences study suggest that functional variation in the neural processing networks supporting immediate reward choice and future-oriented thinking may lead to poorer and better outcomes, respectively, for an evidence-based intervention to reduce adolescent drug misuse. Individual variation in the functional organization of such networks, rather than their level of task engagement, may be particularly predictive of intervention response. The implicated neural networks suggest that interventions that temper learned motivational (IC7) and visceral (IC8) responses to salient rewards (e.g., drugs) or that boost future-oriented thinking (IC12) may offer effective strategies for improving substance use treatment responses among adolescents.

Declaration of Competing Interest

The authors declare no competing financial interests related to this work.

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Clinical trial registration information—The Neuroeconomics of Behavioral Therapies for Adolescent Substance Abuse, http://clinicaltrials.gov/, NCT01093898.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.nicl.2019.101968.

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